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Pharmacology

EIGHTH EDITION

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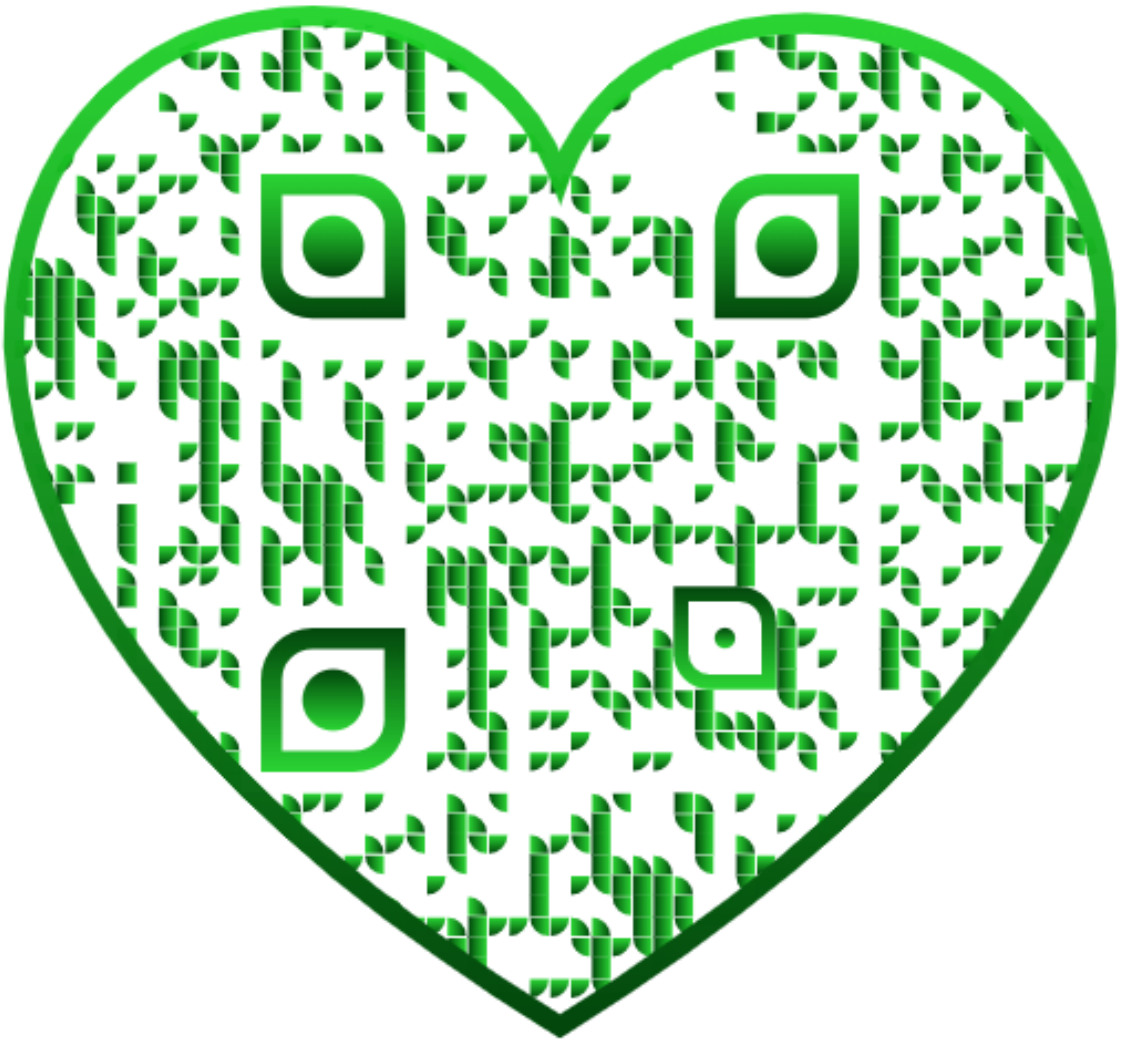

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Lippincott® Illustrated Reviews: Pharmacology

Eighth Edition

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Richard A. Harvey, PhD

1936–2017

Co-creator and series editor of the *Lippincott Illustrated Reviews* series, in collaboration with Pamela C. Champe, PhD (1945–2008).

Illustrator and co-author of the first books in the series: *Biochemistry, Pharmacology, and Microbiology and Immunology*.

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UNIT I:
Principles of Drug Therapy

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1

Pharmacokinetics

Venkata Kashyap Yellepeddi

I. OVERVIEW

Pharmacokinetics refers to what the body does to a drug, whereas pharmacodynamics (see Chapter 2) describes what the drug does to the body. Four pharmacokinetic properties determine the onset, intensity, and duration of drug action (Figure 1.1):

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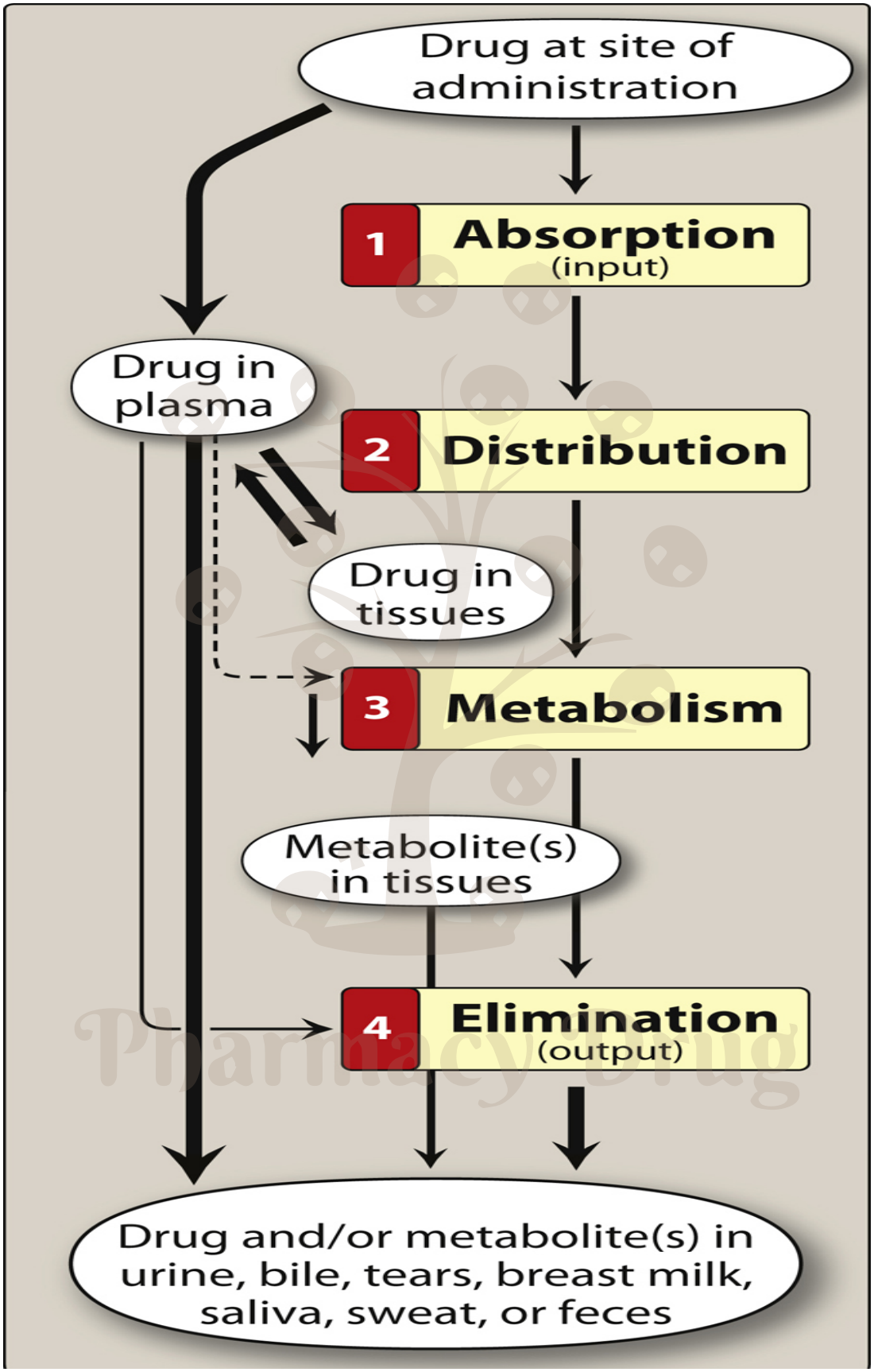

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Figure 1.1 Schematic representation of drug absorption, distribution, metabolism, and elimination.

- **Absorption:** First, absorption from the site of administration permits entry of the drug (either directly or indirectly) into plasma.
- **Distribution:** Second, the drug may reversibly leave the bloodstream and distribute into the interstitial and intracellular fluids.
- **Metabolism:** Third, the drug may be biotransformed through metabolism by the liver or other tissues.
- **Elimination:** Finally, the drug and its metabolites are eliminated from the body in urine, bile, or feces.

Using knowledge of pharmacokinetic parameters, clinicians can design optimal drug regimens, including the route of administration, dose, frequency, and duration of treatment.

II. ROUTES OF DRUG ADMINISTRATION

The route of administration is determined by properties of the drug (for example, water or lipid solubility, ionization) and by the therapeutic objectives (for example, the need for a rapid onset, the need for long-term treatment, or restriction of delivery to a local site). Major routes of drug administration include enteral, parenteral, and topical, among others (Figure 1.2).

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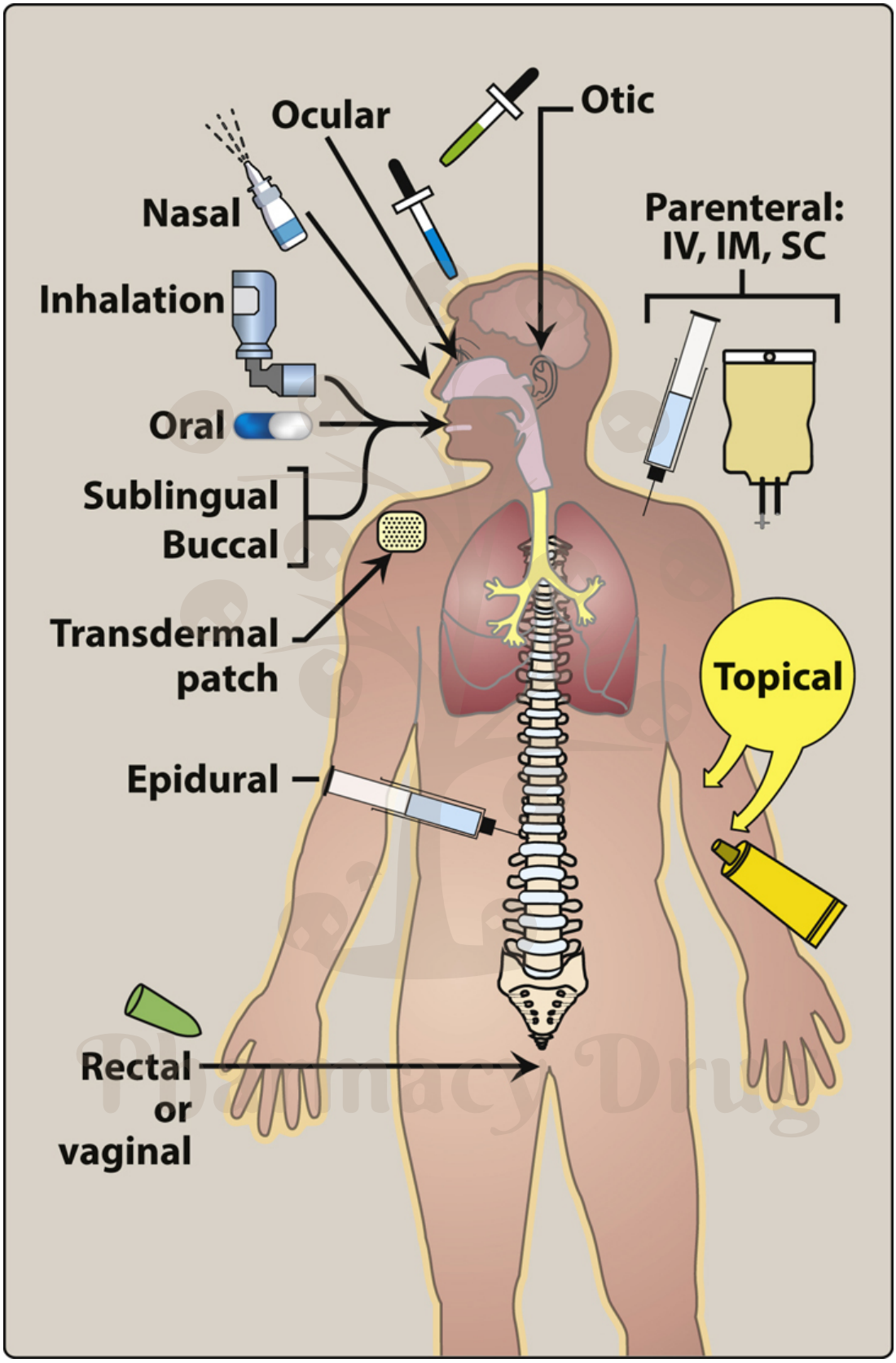

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Figure 1.2 Commonly used routes of drug administration.IV = intravenous; IM = intramuscular; SC = subcutaneous.

A. Enteral

Enteral administration (administering a drug by mouth) is the most common, convenient, and economical method of drug administration. The drug may be swallowed, allowing oral delivery, or it may be placed under the tongue (sublingual) or between the gums and cheek (buccal), facilitating direct absorption into the bloodstream.

1. Oral: Oral administration provides many advantages. Oral drugs are easily self-administered, and toxicities and/or overdose of oral drugs may be overcome with antidotes, such as activated charcoal. However, the pathways involved in oral drug absorption are the most complicated, and the low gastric pH inactivates some drugs. A wide range of oral preparations is available including enteric-coated and extended-release preparations.

    a. Enteric-coated preparations: An enteric coating is a chemical envelope that protects the drug from stomach acid, delivering it instead to the less acidic intestine, where the coating dissolves and releases the drug. Enteric coating is useful for certain drugs (for example, *omeprazole*) that are acid labile, and for drugs that are irritating to the stomach, such as *aspirin*.

    b. Extended-release preparations: Extended-release (abbreviated ER, XR, XL, SR, CR, etc.) medications have special coatings or ingredients that control drug release, thereby allowing for slower absorption and prolonged duration of action. ER formulations can be dosed less frequently and may improve patient compliance. In addition, ER formulations may maintain concentrations within the therapeutic range over a longer duration, as

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opposed to immediate-release dosage forms, which may result in larger peaks and troughs in plasma concentration. ER formulations are advantageous for drugs with short half-lives. For example, the half-life of oral *morphine* is 2 to 4 hours, and it must be administered six times daily to provide continuous pain relief. However, only two doses are needed when extended-release tablets are used.

2. Sublingual/Buccal: The sublingual route involves placement of drug under the tongue. The buccal route involves placement of drug between the cheek and gum. Both the sublingual and buccal routes of absorption have several advantages, including ease of administration, rapid absorption, bypass of the harsh gastrointestinal (GI) environment, and avoidance of first-pass metabolism (see discussion of first-pass metabolism below).

B. Parenteral

The parenteral route introduces drugs directly into the systemic circulation. Parenteral administration is used for drugs that are poorly absorbed from the GI tract (for example, *heparin*) or unstable in the GI tract (for example, *insulin*). Parenteral administration is also used for patients unable to take oral medications (unconscious patients) and in circumstances that require a rapid onset of action. Parenteral administration provides the most control over the dose of drug delivered to the body. However, this route of administration is irreversible and may cause pain, fear, local tissue damage, and infections. The four major parenteral routes are intravascular (intravenous or intra-arterial), intramuscular, subcutaneous, and intradermal (Figure 1.3).

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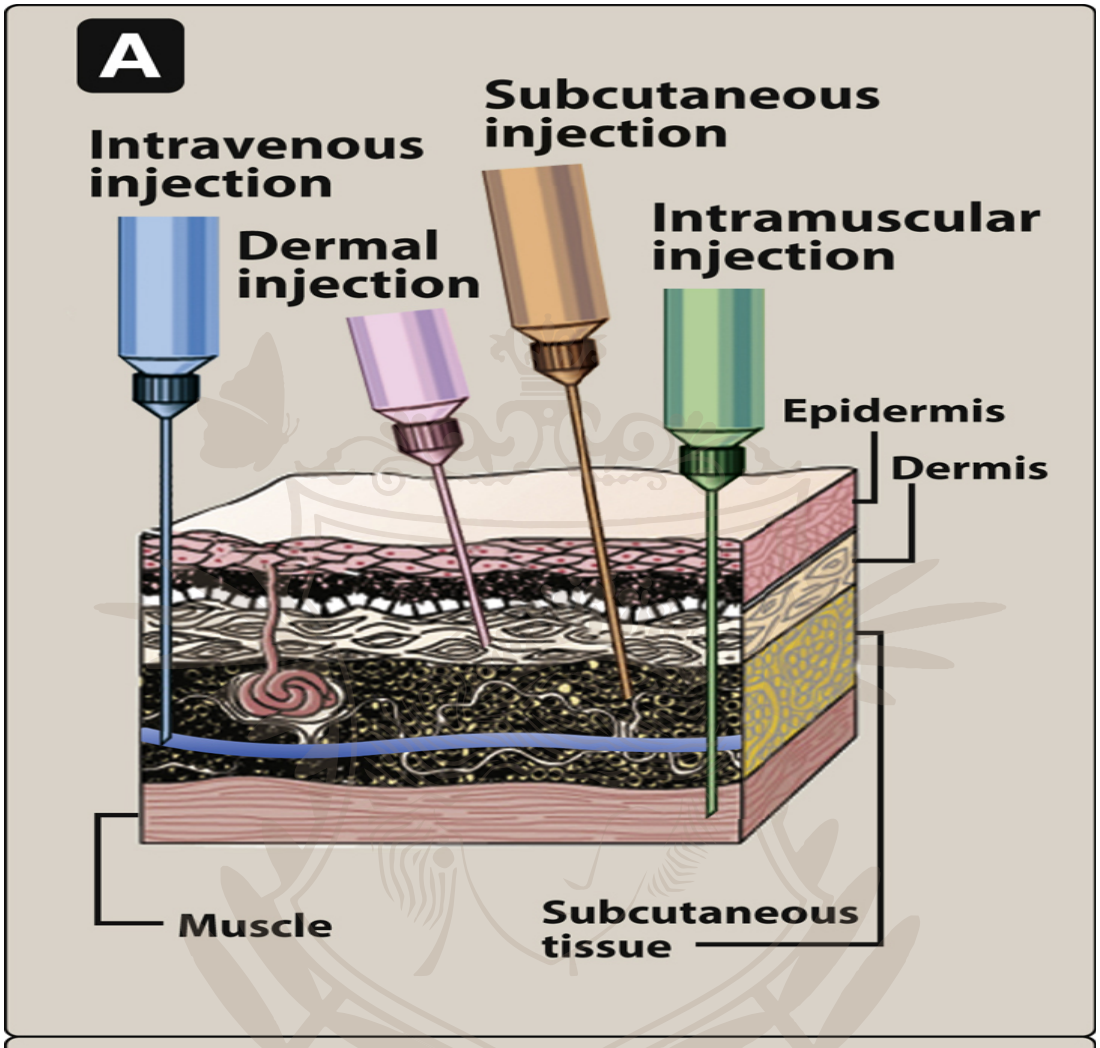
A
Intravenous injection
Subcutaneous injection
Dermal injection
Intramuscular injection
Epidermis
Dermis
Muscle
Subcutaneous tissue

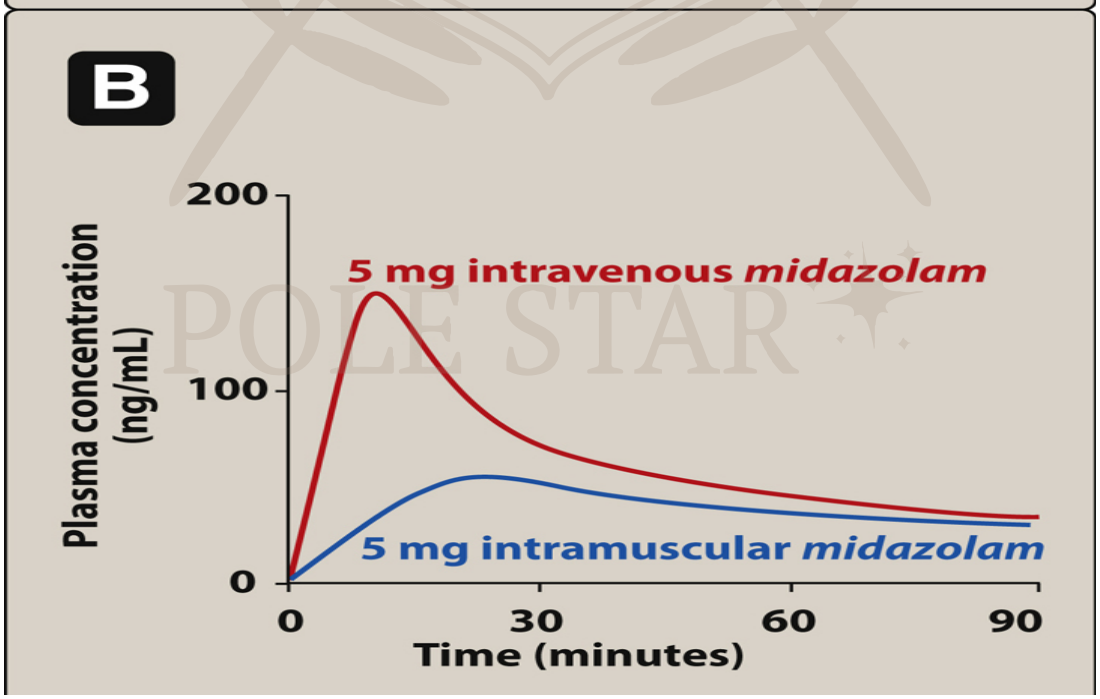
B
Plasma concentration (ng/mL)
200
100
0
5 mg intravenous midazolam
5 mg intramuscular midazolam
0
30
60
90
Time (minutes)

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Figure 1.3 **A.** Schematic representation of subcutaneous and intramuscular injection. **B.** Plasma concentrations of *midazolam* after intravenous and intramuscular injection.

1.Intravenous: Intravenous (IV) injection is the most common parenteral route. It is useful for drugs that are not absorbed orally, such as the neuromuscular blocker *rocuronium.* IV delivery permits a rapid effect and a maximum degree of control over the amount of drug delivered. When injected as a bolus, the full amount of drug is delivered to the systemic circulation almost immediately. If administered as an IV infusion, the drug is infused over a longer period, resulting in lower peak plasma concentrations and an increased duration of circulating drug.

2.Intramuscular: Drugs administered intramuscular (IM) can be in aqueous solutions, which are absorbed rapidly, or in specialized depot preparations, which are absorbed slowly. Depot preparations often consist of a suspension of drug in a nonaqueous vehicle, such as polyethylene glycol or oil. As the vehicle diffuses out of the muscle, drug precipitates at the site of injection. The drug then dissolves slowly, providing a sustained dose over an extended interval.

3.Subcutaneous: Like IM injection, subcutaneous (SC) injection provides absorption via simple diffusion and is slower than the IV route. SC injection minimizes the risks of hemolysis or thrombosis associated with IV injection and may provide constant, slow, and sustained effects. This route should not be used with drugs that cause tissue irritation, because severe pain and necrosis may occur.

4.Intradermal: The intradermal route involves injection into the dermis, the more vascular layer of skin under the

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epidermis. Agents for diagnostic determination and desensitization are usually administered by this route.

C. Other

1. Oral inhalation and nasal preparations: Both the oral inhalation and nasal routes of administration provide rapid delivery of drug across the large surface area of mucous membranes of the respiratory tract and/or pulmonary epithelium. Drug effects are almost as rapid as are those with IV bolus. Drugs that are gases (for example, some anesthetics) and those that can be dispersed in an aerosol are administered via inhalation. This route is effective and convenient for patients with respiratory disorders such as asthma or chronic obstructive pulmonary disease, because drug is delivered directly to the site of action, thereby minimizing systemic side effects. The nasal route involves topical administration of drugs directly into the nose, and it is often used for patients with allergic rhinitis.

2. Intrathecal/Intraventricular: The blood–brain barrier typically delays or prevents the absorption of drugs into the central nervous system (CNS). When local, rapid effects are needed, it is necessary to introduce drugs directly into the cerebrospinal fluid.

3. Topical: Topical application is used when a local effect of the drug is desired.

4. Transdermal: This route of administration achieves systemic effects by application of drugs to the skin, usually via a transdermal patch (Figure 1.4). The rate of absorption can vary markedly, depending on the physical characteristics of the skin at the site of application, as well as the lipid solubility of the drug.

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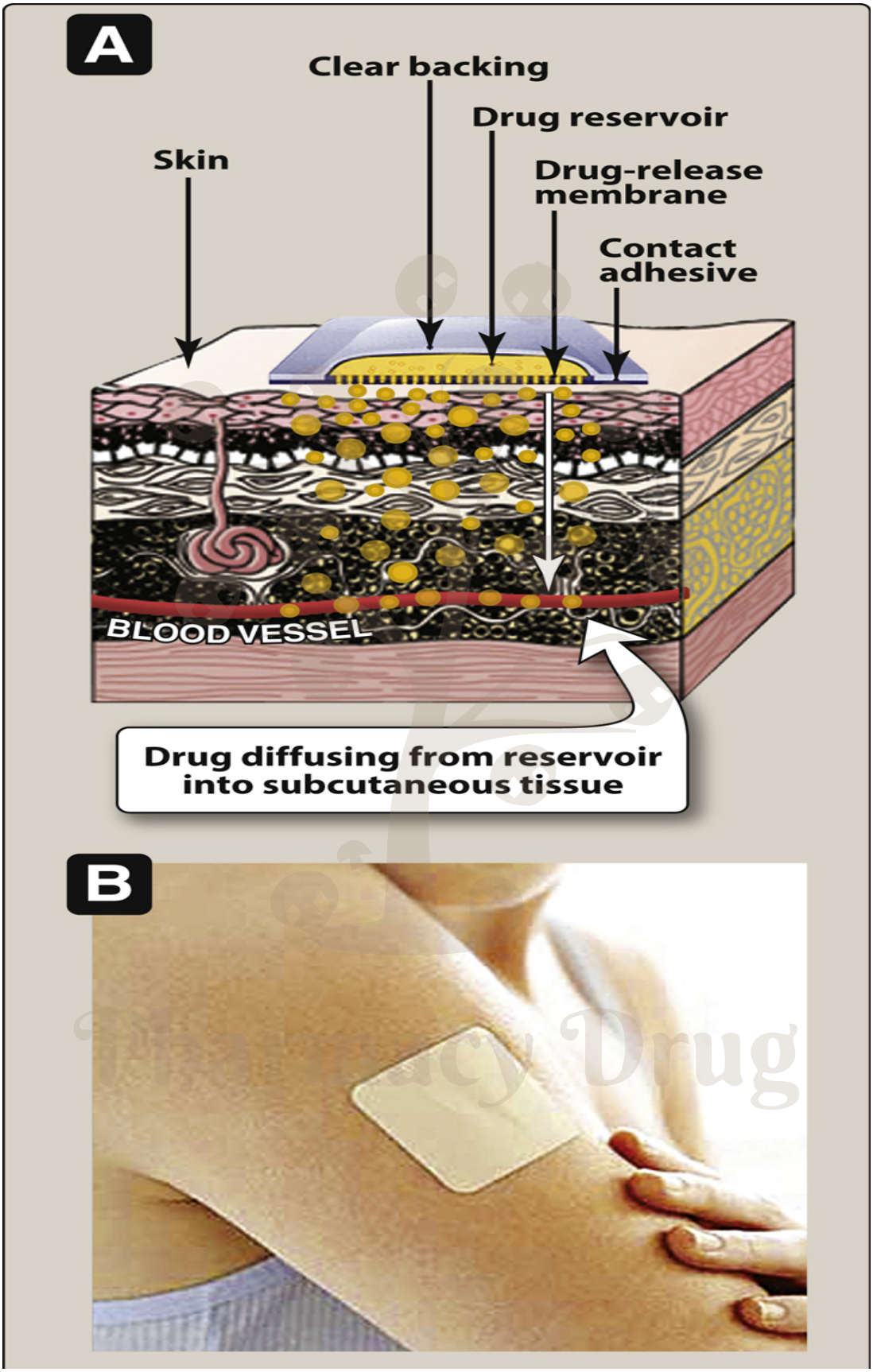

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Figure 1.4 **A.** Schematic representation of a transdermal patch. **B.** Transdermal nicotine patch applied to the arm.

5.Rectal: Because 50% of the drainage of the rectal region bypasses the portal circulation, the biotransformation of drugs by the liver is minimized with rectal administration. The rectal route has the additional advantage of preventing destruction of the drug in the GI environment. This route is also useful if the drug induces vomiting when given orally, if the patient is already vomiting, or if the patient is unconscious. Rectal absorption is often erratic and incomplete, and many drugs irritate the rectal mucosa. Figure 1.5 summarizes characteristics of the common routes of administration, along with example drugs.

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ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES	EXAMPLES
Oral	• Variable; affected by many factors	• Most common, convenient, and economical route of administration	• Limited absorption of some drugs • Food may affect absorption • Patient compliance is necessary • Drugs may be metabolized before systemic absorption	• *Acetaminophen* • *Amoxicillin*
Sublingual	• Depends on the drug: Few drugs (for example, *nitroglycerin*) have rapid, direct systemic absorption Most drugs erratically or incompletely absorbed	• Bypasses first-pass effect • Bypasses destruction by stomach acid • Drug stability maintained because the pH of saliva relatively neutral • May cause immediate pharmacological effects	• Limited to certain types of drugs • Limited to drugs that can be taken in small doses • May lose part of the drug dose if swallowed	• *Nitroglycerin* • *Buprenorphine*
Intravenous	• Absorption not required	• Can have immediate effects • Ideal if dosed in large volumes • Suitable for irritating substances and complex mixtures • Valuable in emergency situations • Dosage titration permissible • Ideal for high molecular weight proteins and peptide drugs	• Unsuitable for oily substances • Most substances must be slowly injected • Strict aseptic techniques needed	• *Vancomycin* • *Heparin*
Intramuscular	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable if drug volume is moderate • Suitable for oily vehicles and certain irritating substances • Preferable to intravenous if patient must self-administer	• Affects certain lab tests (creatine kinase) • Can be painful • Can cause intramuscular hemorrhage (precluded during anticoagulation therapy)	• *Haloperidol* • *Depot medroxy-progesterone*
Subcutaneous	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable for slow-release drugs • Ideal for some poorly soluble suspensions	• Pain or necrosis if drug is irritating • Unsuitable for drugs administered in large volumes	• *Epinephrine* • *Insulin* • *Heparin*
Inhalation	• Systemic absorption may occur; this is not always desirable	• Absorption is rapid; can have immediate effects • Ideal for gases • Effective for patients with respiratory problems • Dose can be titrated • Localized effect to target lungs; lower doses used compared to that with oral or parenteral administration • Fewer systemic side effects	• Most addictive route (drug can enter the brain quickly) • Patient may have difficulty regulating dose • Some patients may have difficulty using inhalers	• *Albuterol* • *Fluticasone*
Topical	• Variable; affected by skin condition, area of skin, and other factors	• Suitable when local effect of drug is desired • May be used for skin, eye, intravaginal, and intranasal products • Minimizes systemic absorption • Easy for patient	• Some systemic absorption can occur • Unsuitable for drugs with high molecular weight or poor lipid solubility	• *Clotrimazole* cream • *Hydrocortisone* cream
Transdermal (patch)	• Slow and sustained	• Bypasses first-pass effect • Convenient and painless • Ideal for drugs that are lipophilic and have poor oral bioavailability • Ideal for drugs that are quickly eliminated from the body	• Some patients are allergic to patches, which can cause irritation • Drug must be highly lipophilic • May cause delayed delivery of drug to pharmacological site of action • Limited to drugs that can be taken in small daily doses	• *Nitroglycerin* • *Nicotine* • *Scopolamine*
Rectal	• Erratic and variable	• Partially bypasses first-pass effect • Bypasses destruction by stomach acid • Ideal if drug causes vomiting • Ideal in patients who are vomiting, or comatose	• Drugs may irritate the rectal mucosa • Not a well-accepted route	• *Bisacodyl* • *Promethazine*

Figure 1.5 The absorption pattern, advantages, and disadvantages of the most common routes of administration.

III. ABSORPTION OF DRUGS

Absorption is the transfer of a drug from the site of administration to the bloodstream. The rate and extent of absorption depend on the

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environment where the drug is absorbed, chemical characteristics of the drug, and the route of administration (which influences bioavailability). Routes of administration other than intravenous may result in partial absorption and lower bioavailability.

A. Mechanisms of absorption of drugs from the GI tract

Depending on their chemical properties, drugs may be absorbed from the GI tract by passive diffusion, facilitated diffusion, active transport, or endocytosis (Figure 1.6).

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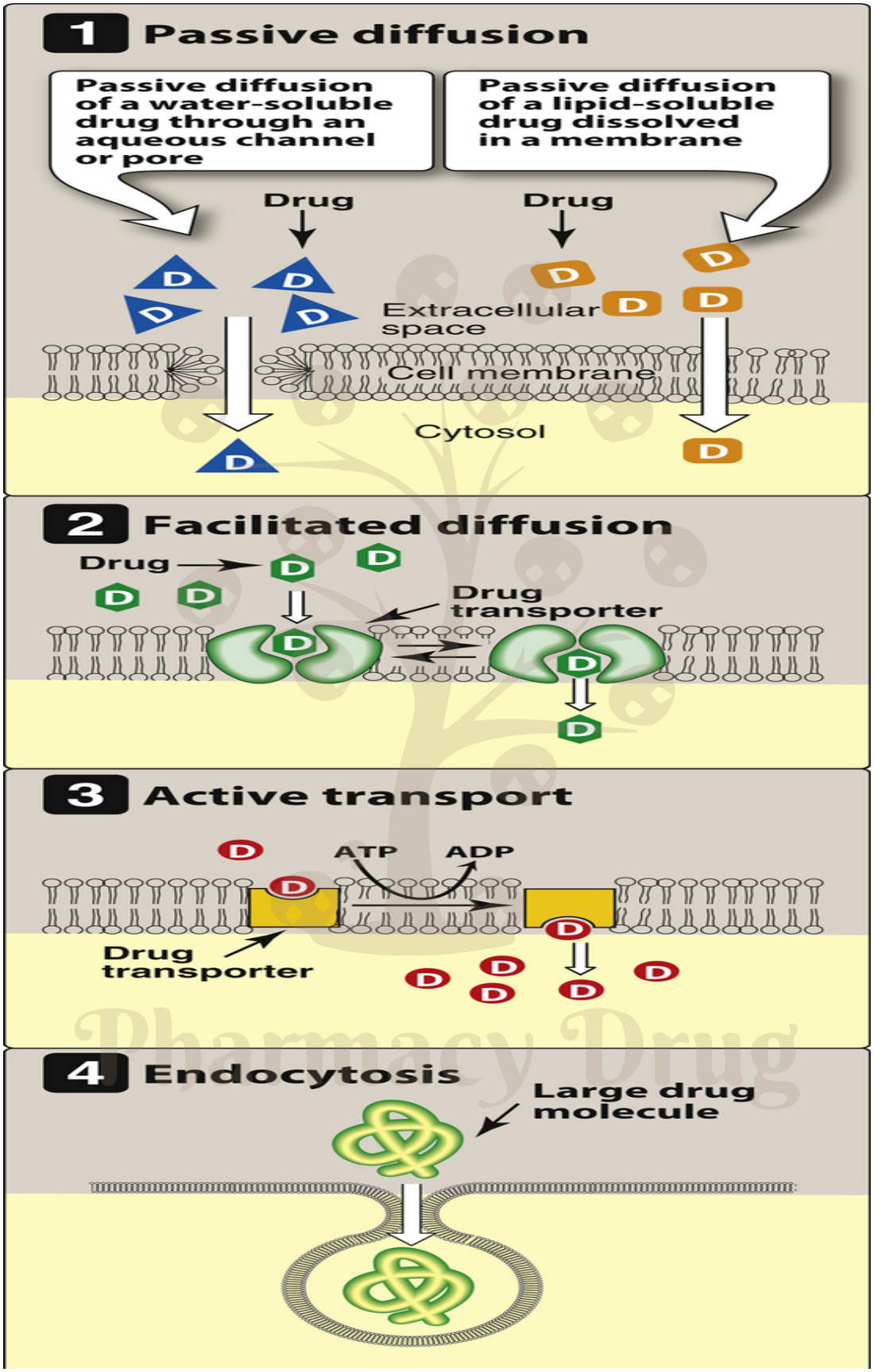

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Figure 1.6 Schematic representation of drugs crossing a cell membrane.ATP = adenosine triphosphate; ADP = adenosine diphosphate.

1.Passive diffusion: The driving force for passive diffusion of a drug is the concentration gradient across a membrane separating two body compartments. In other words, the drug moves from an area of high concentration to one of lower concentration. Passive diffusion does not involve a carrier, is not saturable, and shows low structural specificity. The vast majority of drugs are absorbed by this mechanism. Water-soluble drugs penetrate the cell membrane through aqueous channels or pores, whereas lipid-soluble drugs readily move across most biologic membranes due to solubility in the membrane lipid bilayers.

2.Facilitated diffusion: Other agents can enter the cell through specialized transmembrane carrier proteins that facilitate the passage of large molecules. These carrier proteins undergo conformational changes, allowing the passage of drugs or endogenous molecules into the interior of cells. This process is known as facilitated diffusion. It does not require energy, can be saturated, and may be inhibited by compounds that compete for the carrier.

3.Active transport: This mode of drug entry also involves specific carrier proteins that span the membrane. However, active transport is energy dependent, driven by the hydrolysis of adenosine triphosphate (ATP). It is capable of moving drugs against a concentration gradient, from a region of low drug concentration to one of higher concentration. The process is saturable. Active transport systems are selective and may be competitively inhibited by other cotransported substances.

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4.Endocytosis: This type of absorption is used to transport drugs of exceptionally large size across the cell membrane. Endocytosis involves engulfment of a drug by the cell membrane and transport into the cell by pinching off the drug-filled vesicle. For example, Vitamin B_{12} is transported across the gut wall by endocytosis. [Note: Exocytosis is the reverse of endocytosis. Many cells use exocytosis to secrete substances out of the cell through a similar process of vesicle formation. Certain neurotransmitters (for example, norepinephrine) are stored in intracellular vesicles in the nerve terminal and released by exocytosis.]

B. Factors influencing absorption

1.Effect of pH on drug absorption: Most drugs are either weak acids or weak bases. Acidic drugs (HA) release a proton (H^+), causing a charged anion (A^-) to form:

$$HA \rightleftarrows H^+ + A^-$$

Weak bases (BH^+) can also release an H^+. However, the protonated form of basic drugs is usually charged, and loss of a proton produces the uncharged base (B):

$$BH^+ \rightleftarrows B + H^+$$

A drug passes through membranes more readily if it is uncharged (Figure 1.7). Thus, for a weak acid, the uncharged, protonated HA can permeate through membranes, and A^- cannot. For a weak base, the uncharged form B penetrates through the cell membrane, but the protonated form BH^+ does not. Therefore, the effective concentration of the permeable form of each drug at its absorption site is determined by the relative concentrations of the charged and uncharged forms. The ratio between the two forms is, in turn, determined by the pH at the site of absorption and by the strength of the weak acid or base, which is represented by the ionization constant, pK_a

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(Figure 1.8). [Note: The pK_a is a measure of the strength of the interaction of a compound with a proton. The lower the pK_a of a drug, the more acidic it is. Conversely, the higher the pK_a, the more basic is the drug.] Distribution equilibrium is achieved when the permeable form of a drug achieves an equal concentration in all body water spaces.

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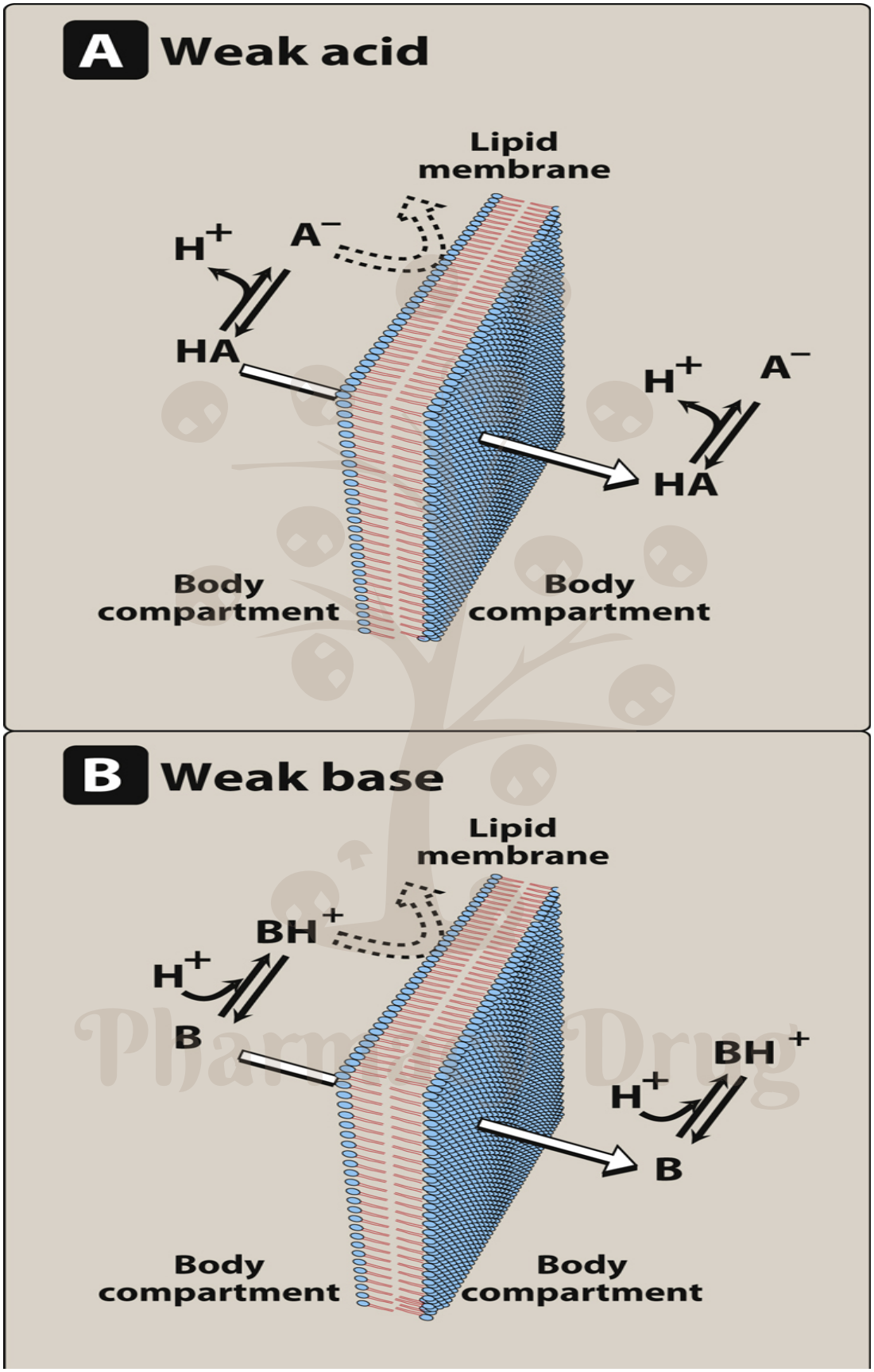

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Figure 1.7 **A.** Diffusion of the nonionized form of a weak acid through a lipid membrane. **B.** Diffusion of the nonionized form of a weak base through a lipid membrane.

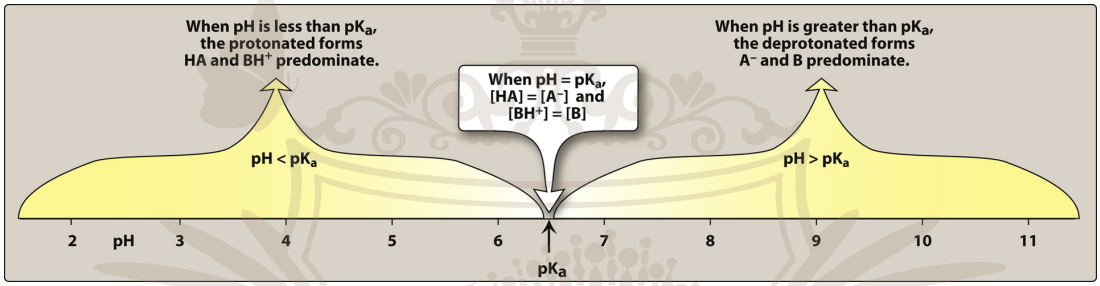

Figure 1.8 The distribution of a drug between its ionized and nonionized forms depends on the ambient pH and pK_a of the drug.For illustrative purposes, the drug has been assigned a pK_a of 6.5.

2.Blood flow to the absorption site: The intestines receive much more blood flow than does the stomach, so absorption from the intestine is favored over the stomach. [Note: Shock severely reduces blood flow to cutaneous tissues, thereby minimizing absorption from SC administration.]

3.Total surface area available for absorption: With a surface rich in brush borders containing microvilli, the intestine has a surface area about 1000-fold that of the stomach, making absorption of the drug across the intestine more efficient.

4.Contact time at the absorption surface: If a drug moves through the GI tract very quickly, as can happen with severe diarrhea, it is not well absorbed. Conversely, anything that delays the transport of the drug from the stomach to the

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intestine delays the rate of absorption. [Note: The presence of food in the stomach both dilutes the drug and slows gastric emptying. Therefore, a drug taken with a meal is generally absorbed more slowly.]

5.Expression of P-glycoprotein: P-glycoprotein is a transmembrane transporter protein responsible for transporting various molecules, including drugs, across cell membranes (Figure 1.9). It is expressed in tissues throughout the body, including the liver, kidneys, placenta, intestines, and brain capillaries, and is involved in transportation of drugs from tissues to blood. That is, it “pumps” drugs out of cells. Thus, in areas of high expression, P-glycoprotein reduces drug absorption. In addition to transporting many drugs out of cells, it is also associated with multidrug resistance.

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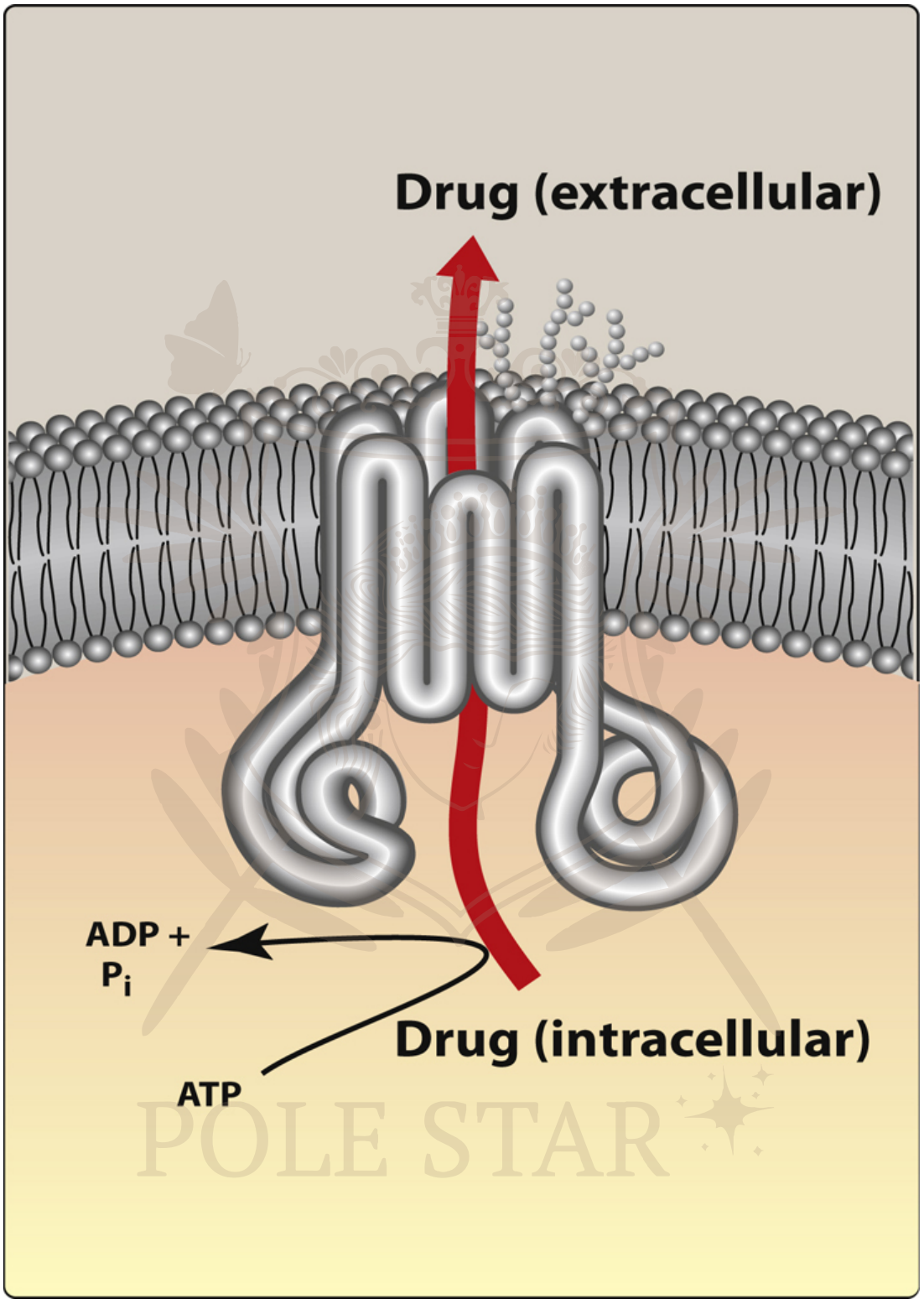

Figure 1.9 The six membrane-spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping of drugs from the cell.

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Clinical Application 1.1: P-glycoprotein and Multidrug Resistance in Cancer

Multidrug resistance (MDR) is a significant obstacle to achieving positive treatment outcomes with chemotherapy in cancer treatment. MDR is caused by overexpression of P-glycoprotein efflux pumps in cancer cells. P-glycoprotein pumps reduce the intracellular accumulation of anticancer drugs such as *paclitaxel*, vinca alkaloids, and anthracyclines (*doxorubicin, daunorubicin*) by effectively pumping drugs out of the cell. The reduced accumulation of chemotherapeutic drugs in cancer cells leads to resistance and ultimately results in poor prognoses in various cancers. P-glycoprotein-mediated MDR in cancer can be overcome by co-administering P-glycoprotein pump inhibitors with chemotherapeutic agents. Unfortunately, there are no approved P-glycoprotein inhibitors for clinical use in cancer chemotherapy to reverse MDR. However, several clinical trials are currently investigating the usefulness of co-administering P-glycoprotein pump inhibitors with anticancer drugs such as *paclitaxel, docetaxel, doxorubicin, and vinorelbine* to reverse MDR in various cancers.

C. Bioavailability

Bioavailability is the rate and extent to which an administered drug reaches the systemic circulation. For example, if 100 mg of a drug is administered orally and 70 mg is absorbed unchanged, the bioavailability is 0.7 or 70%. Determining bioavailability is important for calculating drug dosages for nonintravenous routes of administration.

1. **Determination of bioavailability:** Bioavailability is determined by comparing plasma levels of a drug after a particular route of administration (for example, oral administration) with levels achieved by IV administration. After IV administration, 100% of the drug rapidly enters the circulation. When the drug is given orally, only part of the administered dose appears in the plasma. By plotting plasma concentrations of the drug versus time, the area under the

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curve (AUC) can be measured. A schematic depiction of determination of bioavailability is provided in Figure 1.10.

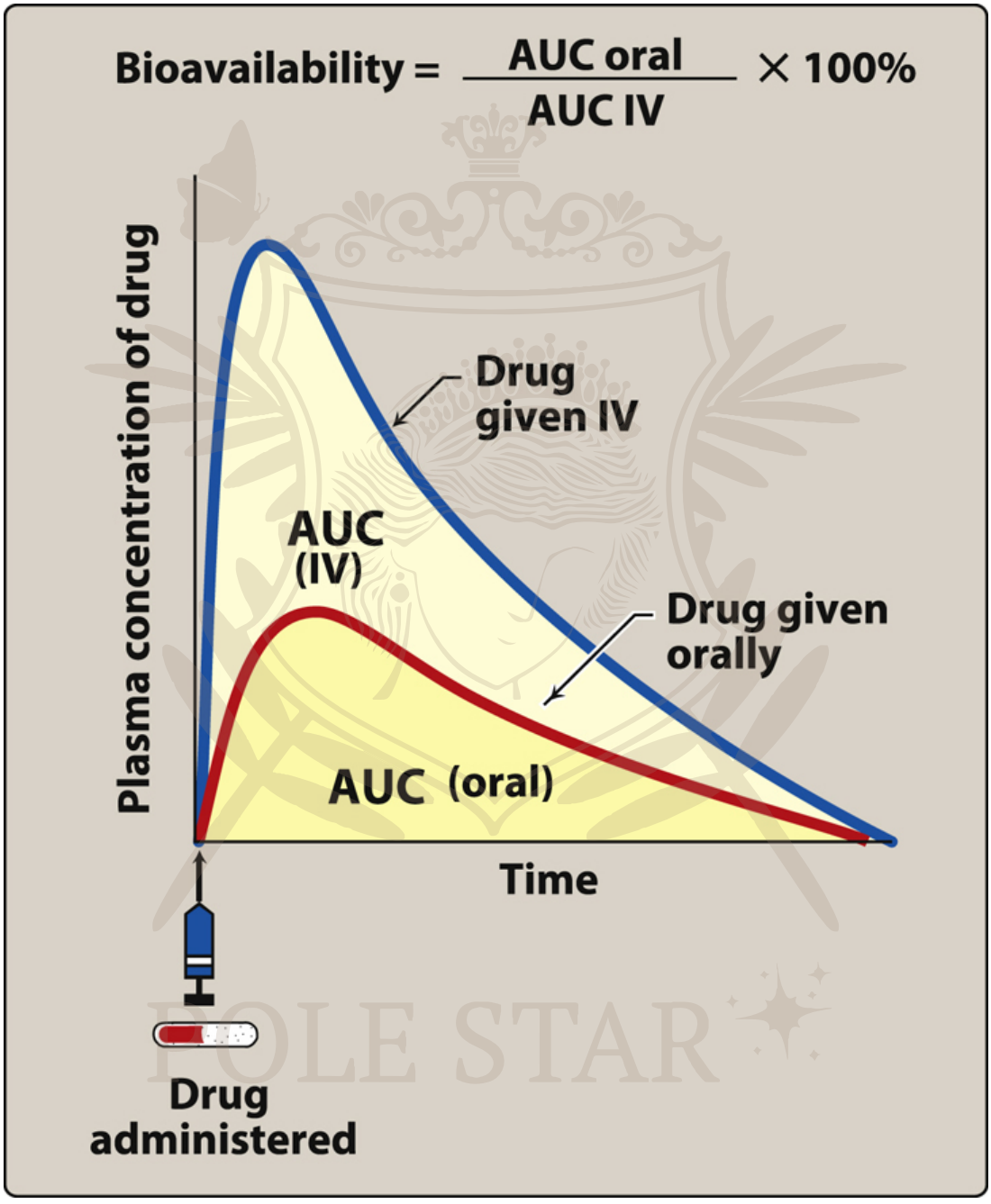

Figure 1.10 Determination of the bioavailability of a drug.AUC = area under curve; IV = intravenous.

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2.Factors that influence bioavailability: In contrast to IV administration, which confers 100% bioavailability, orally administered drugs often undergo first-pass metabolism. This biotransformation, in addition to chemical and physical characteristics of the drug, determines the rate and extent to which the agent reaches the systemic circulation.

a. First-pass hepatic metabolism: When a drug is absorbed from the GI tract, it enters the portal circulation before entering the systemic circulation (Figure 1.11). If the drug is rapidly metabolized in the liver or gut wall during this initial passage, the amount of unchanged drug entering the systemic circulation is decreased. This is referred to as first-pass metabolism. [Note: First-pass metabolism by the intestine or liver limits the efficacy of many oral medications. For example, more than 90% of *nitroglycerin* is cleared during first-pass metabolism. Hence, it is primarily administered via the sublingual, transdermal, or intravenous route.] Drugs with high first-pass metabolism should be given in doses sufficient to ensure that enough active drug reaches the desired site of action.

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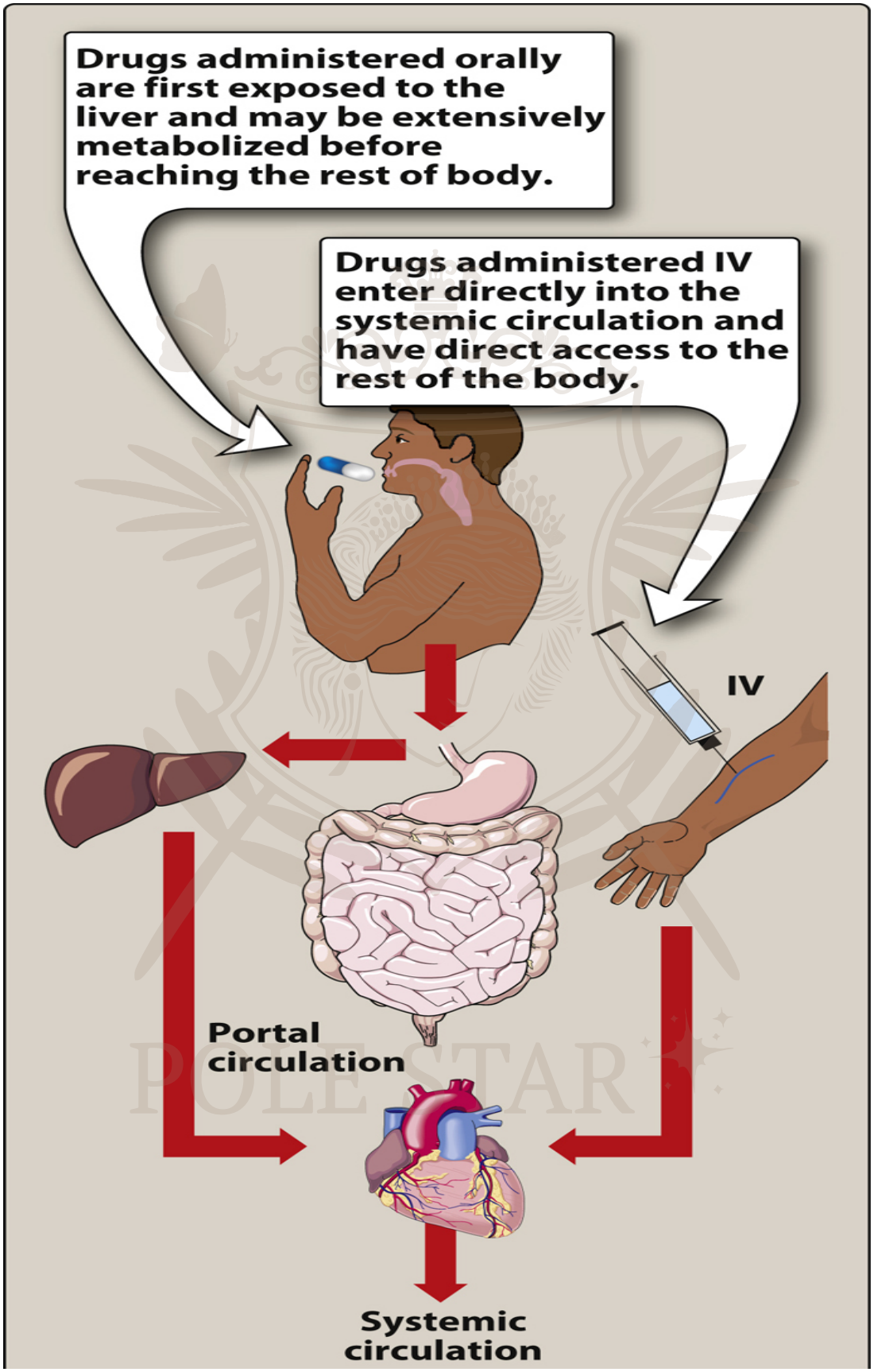
Drugs administered orally are first exposed to the liver and may be extensively metabolized before reaching the rest of body.
Drugs administered IV enter directly into the systemic circulation and have direct access to the rest of the body.
IV
Portal circulation
Systemic circulation

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Figure 1.11 First-pass metabolism can occur with orally administered drugs.IV = intravenous.

b. Solubility of the drug: Very hydrophilic drugs are poorly absorbed because of the inability to cross lipid-rich cell membranes. Paradoxically, drugs that are extremely lipophilic are also poorly absorbed, because they are insoluble in aqueous body fluids and, therefore, cannot gain access to the surface of cells. For a drug to be readily absorbed, it must be largely lipophilic, yet have some solubility in aqueous solutions. This is one reason why many drugs are either weak acids or weak bases.

c. Chemical instability: Some drugs, such as *penicillin G*, are unstable in the pH of gastric contents. Others, such as *insulin*, are destroyed in the GI tract by degradative enzymes.

d. Nature of the drug formulation: Drug absorption may be altered by factors unrelated to the chemistry of the drug. For example, particle size, salt form, crystal polymorphism, enteric coatings, and the presence of excipients (such as binders and dispersing agents) can influence the ease of dissolution and, therefore, alter the rate of absorption.

D. Bioequivalence and other types of equivalence

Two drug formulations are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations. Two drug formulations are therapeutically equivalent if they are pharmaceutically equivalent (that is, they have the same dosage form, contain the same active ingredient at the same strength, and use the same route of administration) with similar clinical and safety profiles. Thus, therapeutic equivalence

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requires that drug products are bioequivalent and pharmaceutically equivalent.

IV. DRUG DISTRIBUTION

Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the extracellular fluid and tissues. For drugs administered IV, absorption is not a factor, and the initial phase immediately following administration represents the distribution phase, during which the drug rapidly leaves the circulation and enters the tissues (Figure 1.12). The distribution of a drug from the plasma to the interstitium depends on cardiac output and local blood flow, capillary permeability, tissue volume, degree of binding of the drug to plasma and tissue proteins, and relative lipophilicity of the drug.

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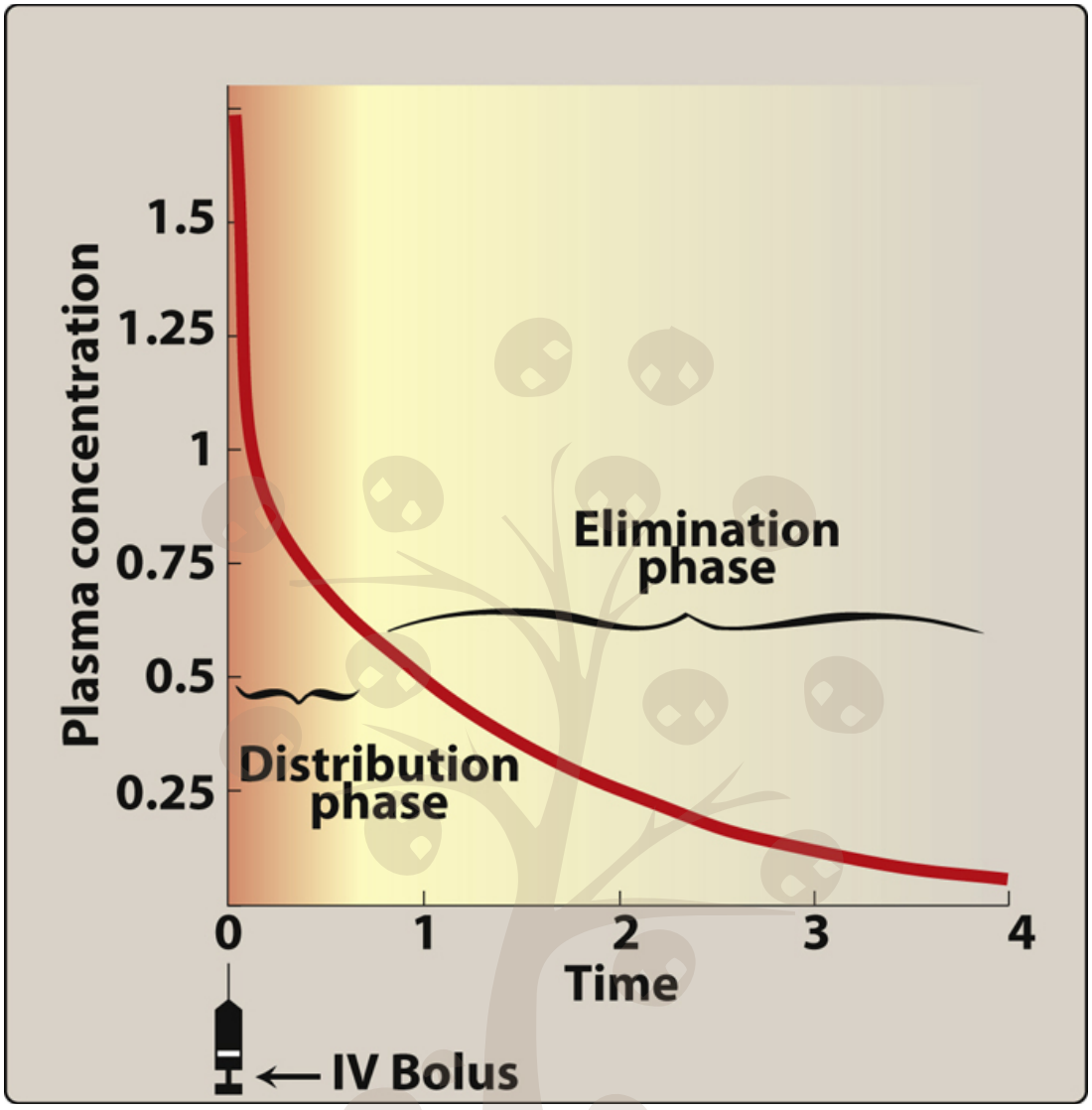

Figure 1.12 Drug concentrations in serum after a single injection of drug.Assume that the drug distributes and is subsequently eliminated.

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A. Blood flow

The rate of blood flow to the tissue capillaries varies widely. For instance, blood flow to "vessel-rich organs" (brain, liver, and kidney) is greater than that to the skeletal muscles. Adipose tissue, skin, and viscera have still lower rates of blood flow. Variation in blood flow partly explains the short duration of hypnosis produced by an IV bolus of *propofol* (see Chapter 20).

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High blood flow, together with high lipophilicity of *propofol*, permits rapid distribution into the CNS and produces anesthesia. A subsequent slower distribution to skeletal muscle and adipose tissue lowers the plasma concentration so that the drug diffuses out of the CNS, down the concentration gradient, and consciousness is regained.

B. Capillary permeability

Capillary permeability is determined by capillary structure and by the chemical nature of the drug. Capillary structure varies in terms of the fraction of the basement membrane exposed by slit junctions between endothelial cells. In the liver and spleen, a significant portion of the basement membrane is exposed due to large, discontinuous capillaries through which large plasma proteins can pass (Figure 1.13A). In the brain, the capillary structure is continuous, and there are no slit junctions (Figure 1.13B). To enter the brain, drugs must pass through the endothelial cells of the CNS capillaries or undergo active transport. For example, a specific transporter carries *levodopa* into the brain. Lipid-soluble drugs readily penetrate the CNS because they dissolve in the endothelial cell membrane. By contrast, ionized or polar drugs generally fail to enter the CNS because they cannot pass through the endothelial cells that have no slit junctions (Figure 1.13C). These closely juxtaposed cells form tight junctions that constitute the blood–brain barrier.

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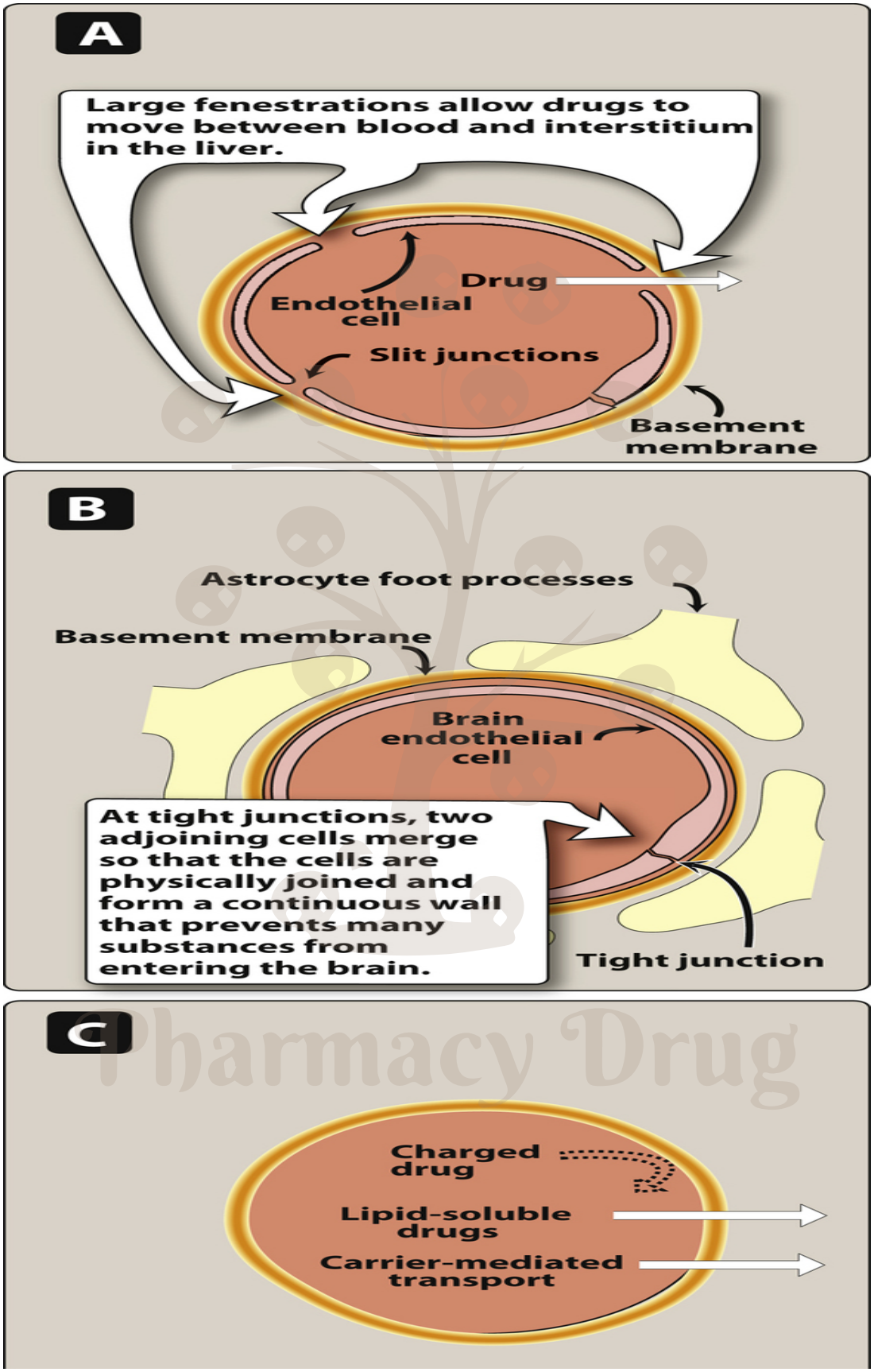

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Figure 1.13 Cross section of liver and brain capillaries.**A.** Structure of liver capillary. **B.** Structure of a brain capillary. **C**. Permeability of a brain capillary.

C. Binding of drugs to plasma proteins and tissues

1. **Binding to plasma proteins:** Reversible binding to plasma proteins sequesters drugs in a nondiffusible form and slows transfer out of the vascular compartment. Albumin is the major drug-binding protein, and it may act as a drug reservoir. As the concentration of free drug decreases due to elimination, the bound drug dissociates from albumin. This maintains the free-drug concentration as a constant fraction of the total drug in the plasma.

2. **Binding to tissue proteins:** Many drugs accumulate in tissues, leading to higher concentrations in tissues than in interstitial fluid and blood. Drugs may accumulate because of binding to lipids, proteins, or nucleic acids. Drugs may also undergo active transport into tissues. Tissue reservoirs may serve as a major source of the drug and prolong its actions or cause local drug toxicity. (For example, acrolein, the metabolite of *cyclophosphamide*, can cause hemorrhagic cystitis because it accumulates in the bladder.)

D. Lipophilicity

The chemical nature of a drug strongly influences its ability to cross cell membranes. Lipophilic drugs readily move across most biologic membranes. These drugs dissolve in the lipid membranes and penetrate the entire cell surface. The major factor influencing the distribution of lipophilic drugs is blood flow to the area. By contrast, hydrophilic drugs do not readily penetrate cell membranes and must pass through slit junctions.

E. Volume of distribution

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The apparent volume of distribution, V_d, is defined as the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma. It is calculated by dividing the dose that ultimately gets into the systemic circulation by the plasma concentration at time zero (C_0).

$$V_d = \frac{\text{Amount of drug in the body}}{C_o}$$

Although V_d has no physiologic or physical basis, it can be useful to compare the distribution of a drug with the volumes of the water compartments in the body.

1. Distribution into the water compartments in the body: Once a drug enters the body, it has the potential to distribute into any one of the three functionally distinct compartments of body water or to become sequestered in a cellular site.

a. Plasma compartment: If a drug has a high molecular weight or is extensively protein bound, it is too large to pass through the slit junctions of the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment. As a result, it has a low V_d that approximates the plasma volume, or about 4 L in a 70-kg individual. *Heparin* (see Chapter 13) shows this type of distribution.

b. Extracellular fluid: If a drug has a low molecular weight but is hydrophilic, it can pass through the endothelial slit junctions of the capillaries into the interstitial fluid. However, hydrophilic drugs cannot move across the lipid membranes of cells to enter the intracellular fluid. Therefore, these drugs distribute into a volume that is the sum of the plasma volume and the interstitial fluid, which together constitute the extracellular fluid (about 20% of

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body weight or 14 L in a 70-kg individual). Aminoglycoside antibiotics (see Chapter 30) show this type of distribution.

c. Total body water: If a drug has a low molecular weight and has enough lipophilicity, it can move into the interstitium through the slit junctions and pass through the cell membranes into the intracellular fluid. These drugs distribute into a volume of about 60% of body weight or about 42 L in a 70-kg individual. *Ethanol* exhibits this apparent V_d. [Note: In general, a larger V_d indicates greater distribution into tissues; a smaller V_d suggests confinement to plasma or extracellular fluid.]

2. Determination of V_d: The fact that drug clearance is usually a first-order process allows calculation of V_d. First order means that a constant fraction of the drug is eliminated per unit of time. This process can be most easily analyzed by plotting the log of the plasma drug concentration (C_p) versus time (Figure 1.14). The concentration of drug in the plasma can be extrapolated back to time zero (the time of IV bolus) on the Y axis to determine C_0, which is the concentration of drug that would have been achieved if the distribution phase had occurred instantly. This allows calculation of V_d as:

$$V_d = \frac{\text{Dose}}{C_0}$$

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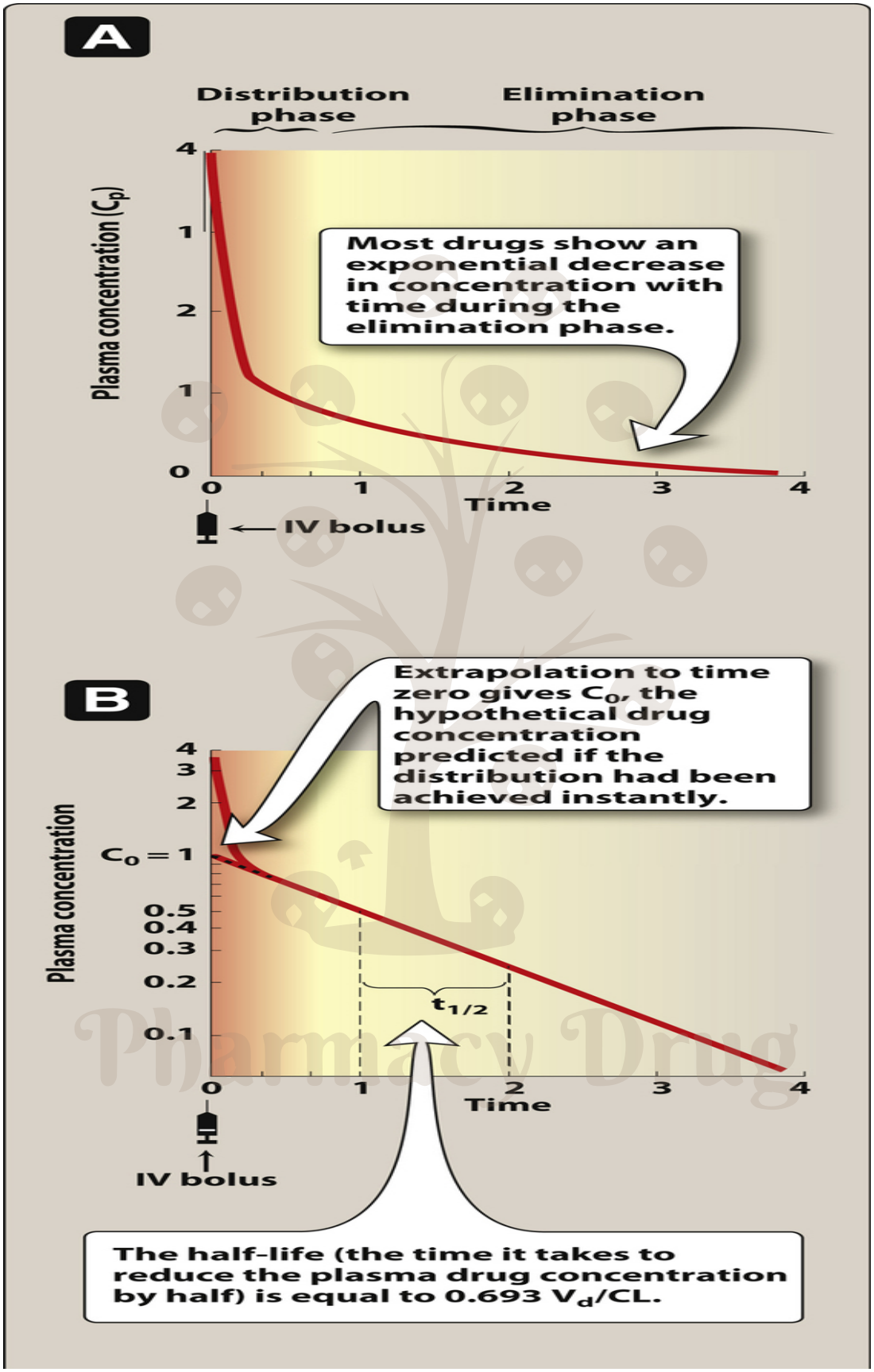

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Figure 1.14 Drug concentrations in plasma after a single injection of drug at time = 0.**A.** Concentration data are plotted on a linear scale. **B.** Concentration data are plotted on a log scale.

For example, if 10 mg of drug is injected into a patient and the plasma concentration is extrapolated back to time zero, and C_0 = 1 mg/L (from the graph in Figure 1.14B), then V_d = 10 mg/1 mg/L = 10 L.

3.Effect of V_d on drug half-life: V_d has an important influence on the half-life of a drug, because drug elimination depends on the amount of drug delivered to the liver or kidney (or other organs where metabolism occurs) per unit of time. Delivery of drug to the organs of elimination depends not only on blood flow but also on the fraction of drug in the plasma. If a drug has a large V_d, most of the drug is in the extraplasmic space and is unavailable to the excretory organs. Therefore, any factor that increases V_d can increase the half-life and extend the duration of action of the drug. [Note: An exceptionally large V_d indicates considerable sequestration of the drug in some tissues or compartments.]

V. DRUG CLEARANCE THROUGH METABOLISM

Once a drug enters the body, the process of elimination begins. The three major routes of elimination are hepatic metabolism, biliary elimination, and urinary excretion. [Note: Elimination is irreversible removal of drug from the body. It involves biotransformation (drug metabolism) and excretion. Excretion is removal of intact drug from the body.] Together, these elimination processes decrease the plasma concentration exponentially. That is, a constant fraction of the drug is eliminated in a given unit of time (Figure 1.14A).

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Metabolism results in products with increased polarity, which allows the drug to be eliminated. Clearance (CL) estimates the volume of blood from which the drug is cleared per unit of time. Total CL is a composite estimate reflecting all mechanisms of drug elimination and is calculated as follows:

$$CL = 0.693 \times V_d / t_{1/2}$$

where $t_{1/2}$ is the elimination half-life, V_d is the apparent volume of distribution, and 0.693 is the natural log constant. Drug half-life is often used as a measure of drug CL, because, for many drugs, V_d is a constant.

A. Kinetics of metabolism

1.First-order kinetics: The metabolic transformation of drugs is catalyzed by enzymes, and most of the reactions obey Michaelis–Menten kinetics, where K_m is Michaelis constant (the substrate concentration at half maximal velocity).

$$v = \text{Rate of drug metabolism} = \frac{V_{max}[C]}{K_m + [C]}$$

In most clinical situations, the concentration of the drug, [C], is much less than the Michaelis constant, K_m, and the Michaelis–Menten equation reduces to:

$$v = \text{Rate of drug metabolism} = \frac{V_{max}[C]}{K_m}$$

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That is, the rate of drug metabolism and elimination is directly proportional to the concentration of free drug, and first-order kinetics is observed (Figure 1.15). This means that a constant fraction of drug is metabolized per unit of time (that is, with each half-life, the concentration decreases by 50%). First-order kinetics is also referred to as linear kinetics.

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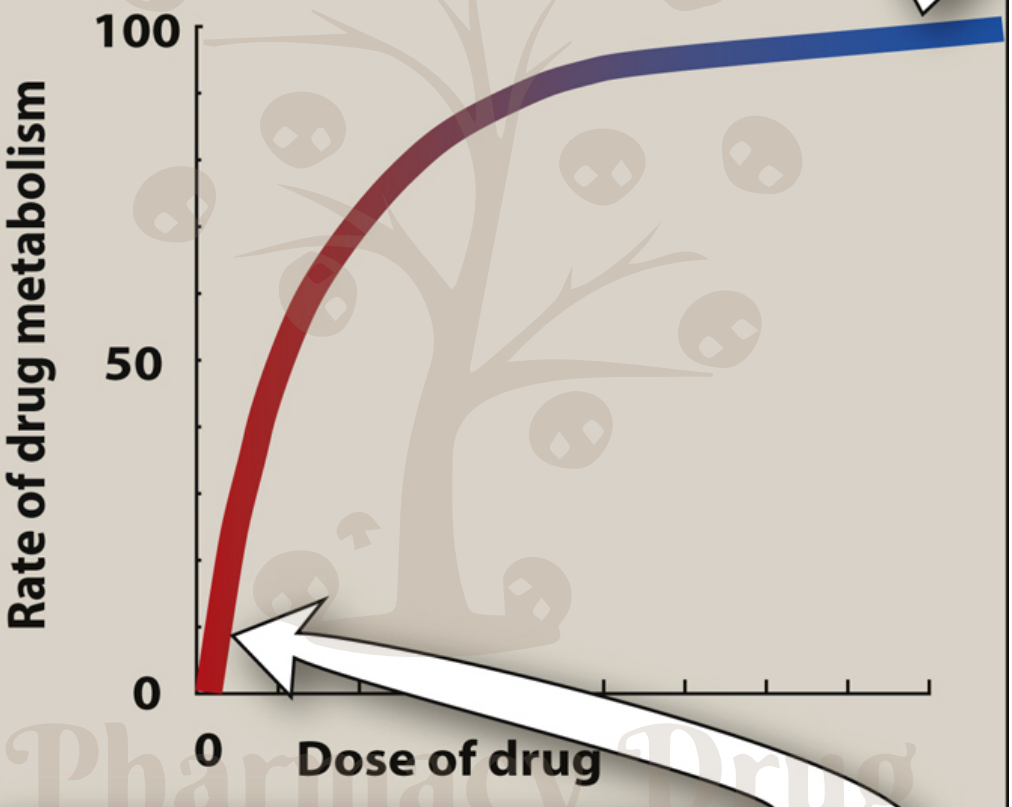
With a few drugs, such as *aspirin*, *ethanol*, and *phenytoin*, the doses are very large. Therefore, the plasma drug concentration is much greater than K_m, and drug metabolism is **zero order**, that is, constant and independent of the drug dose.



With most drugs the plasma drug concentration is less than K_m, and drug elimination is **first order**, that is, proportional to the drug dose.

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Figure 1.15 Effect of drug dose on the rate of metabolism.

2.Zero-order kinetics: With a few drugs, such as *aspirin*, *ethanol*, and *phenytoin*, the doses are very large. Therefore, [C] is much greater than K_m, and the velocity equation becomes:

$$v = \text{Rate of drug metabolism} = \frac{V_{max}[C]}{[C]} = V_{max}$$

The enzyme is saturated by a high free drug concentration, and the rate of metabolism remains constant over time. This is called zero-order kinetics (also called nonlinear kinetics). A constant amount of drug is metabolized per unit of time. The rate of elimination is constant and does not depend on the drug concentration.

B. Reactions of drug metabolism

The kidney cannot efficiently excrete lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal convoluted tubules. Therefore, lipid-soluble agents are first metabolized into more polar (hydrophilic) substances in the liver via two general sets of reactions, called phase I and phase II (Figure 1.16).

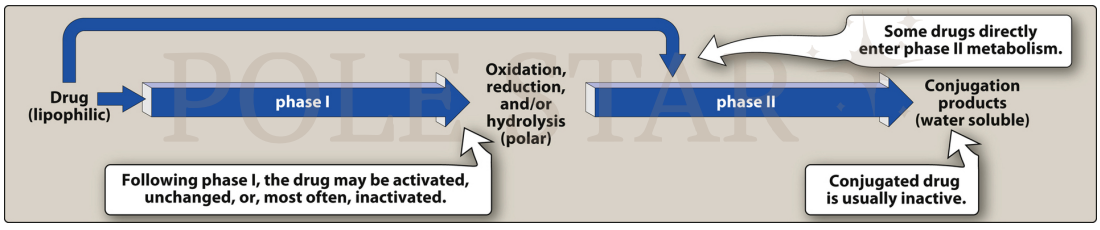

Figure 1.16 The biotransformation of drugs.

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1.Phase I: Phase I reactions convert lipophilic drugs into more polar molecules by introducing or unmasking a polar functional group, such as –OH or $–NH_2$. Phase I reactions usually involve reduction, oxidation, or hydrolysis. Phase I metabolism may increase, decrease, or have no effect on pharmacologic activity.

a. Phase I reactions utilizing the P450 system: The phase I reactions most frequently involved in drug metabolism are catalyzed by the cytochrome P450 (CYP) system. The P450 system is important for the metabolism of many endogenous compounds (such as steroids, lipids) and for the biotransformation of exogenous substances (drugs, carcinogens, and environmental pollutants). CYP is a superfamily of heme-containing isozymes located in most cells, but primarily in the liver and GI tract.

[1] Nomenclature: The family name is indicated by the Arabic number that follows CYP, and the capital letter designates the subfamily, for example, CYP3A (Figure 1.17). A second number indicates the specific isozyme, as in CYP3A4.

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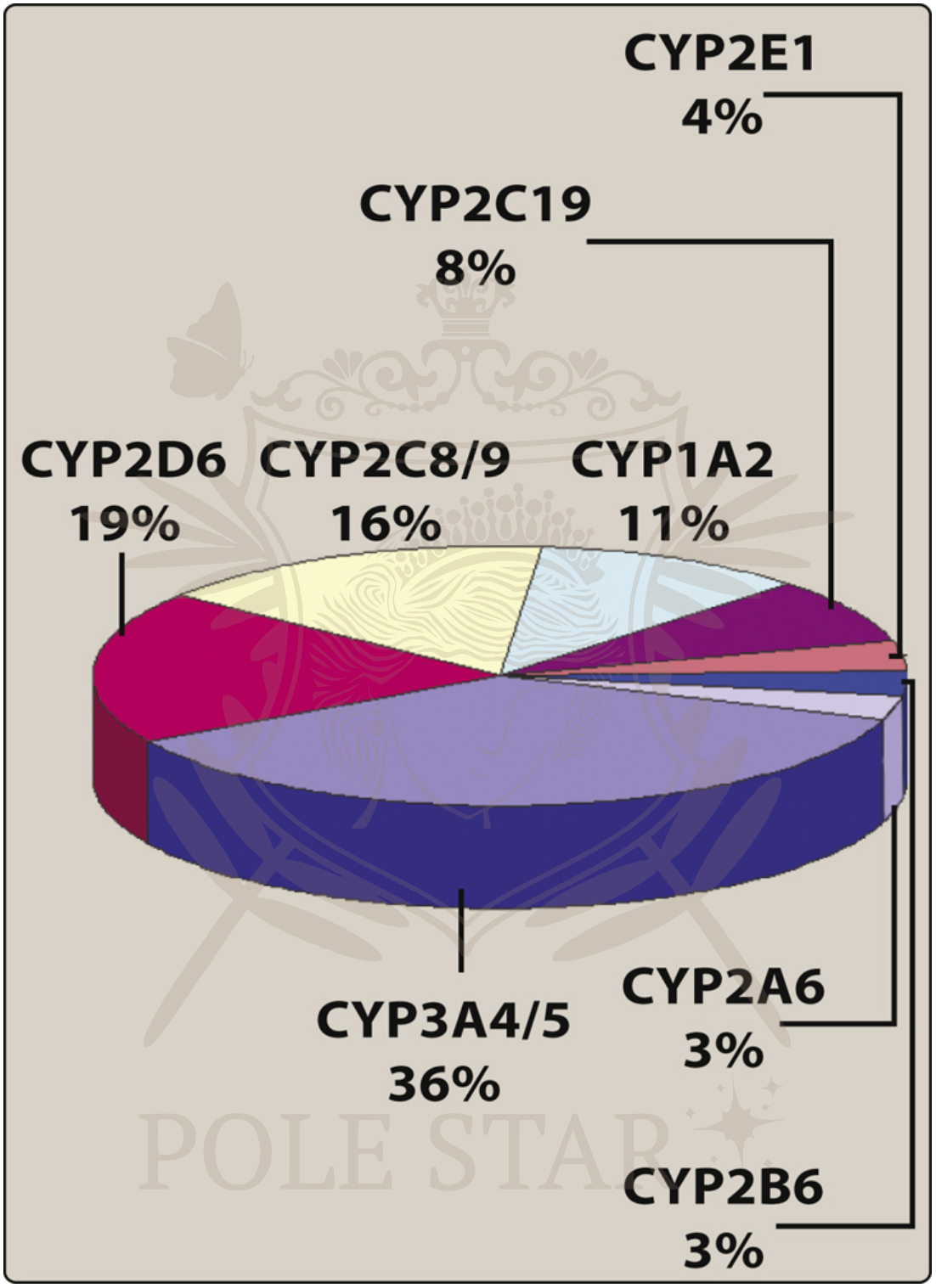

Figure 1.17 Relative contribution of cytochrome P450 (CYP) isoforms to drug biotransformation.

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[2] Specificity: Because there are many different genes that encode multiple enzymes, there are many different P450 isoforms. These enzymes have the capacity to modify a large number of structurally diverse substrates. In addition, an individual drug may be a substrate for more than one isozyme. Four isozymes (CYP3A4/5, CYP2D6, CYP2C8/9, and CYP1A2) are responsible for the vast majority of P450-catalyzed reactions (Figure 1.17). Considerable amounts of CYP3A4 are found in intestinal mucosa, accounting for first-pass metabolism of drugs such as *cyclosporine* and *midazolam.*

[3] Genetic variability: P450 enzymes exhibit considerable genetic variability among individuals and racial groups. Variations in P450 activity may alter drug efficacy and the risk of adverse events. CYP2D6, in particular, exhibits genetic polymorphism. CYP2D6 mutations result in very low capacities to metabolize substrates. For example, some individuals obtain no benefit from the opioid analgesic *codeine*, because they lack the CYP2D6 enzyme that activates the drug. Similar polymorphisms have been characterized for the CYP2C subfamily of isozymes. For instance, *clopidogrel* carries a warning that patients who are CYP2C19 "poor metabolizers" have a diminished antiplatelet effect when taking this drug and an alternative medication should be considered. *Clopidogrel* is a prodrug, and CYP2C19 activity is required to convert it to the active metabolite.

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Clinical Application 1.2: Codeine Overdose in Infants of Breastfeeding Mothers

Codeine is a pain killer that is metabolized in the liver to *morphine* by CYP2D6 enzymes. The Food and Drug Administration (FDA) reviewed medical literature for data regarding *codeine* use during breastfeeding and found several cases of excessive sleepiness and respiratory failure, including one death in infants of

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breastfeeding mothers taking *codeine.* Upon further investigation, FDA found that some of the breastfeeding mothers had a variation of CYP2D6 enzyme that metabolizes *codeine* to *morphine* faster and to a greater extent than in others. These individuals are called CYP2D6 ultrarapid metabolizers. Therefore, in breastfeeding mothers who are CYP2D6 ultrarapid metabolizers, the ultrarapid conversion of *codeine* to *morphine* results in high and unsafe levels of *morphine* in breast milk and can lead to *morphine* overdose in breastfeeding infants. FDA ultimately issued a warning to breastfeeding mothers to avoid *codeine* use due to the risk of life-threatening adverse events of *morphine* overdose in infants.

[4] CYP inducers: The CYP450-dependent enzymes are an important target for pharmacokinetic drug interactions. Certain drugs (for example, *phenobarbital*, *rifampin*, and *carbamazepine*) are capable of inducing CYP isozymes. This results in increased biotransformation of drugs and can lead to significant decreases in plasma concentrations of drugs metabolized by these CYP isozymes, often with concurrent loss of pharmacologic effect. For example, *rifampin*, an antituberculosis drug (see Chapter 32), significantly decreases the plasma concentrations of human immunodeficiency virus (HIV) protease inhibitors, thereby diminishing the ability to suppress HIV replication. Figure 1.18 lists some of the more important inducers for representative CYP isozymes.

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Isozyme: CYP2C9

COMMON SUBSTRATES	INDUCERS
Celecoxib	*Carbamazepine*
Glimepiride	*Phenobarbital*
Ibuprofen	*Rifampin*
Phenytoin	
Warfarin	

Isozyme: CYP2D6

COMMON SUBSTRATES	INDUCERS
Fluoxetine	None*
Haloperidol	
Paroxetine	
Propranolol	

Isozyme: CYP3A4/5

COMMON SUBSTRATES	INDUCERS
Carbamazepine	*Carbamazepine*
Cyclosporine	*Dexamethasone*
Erythromycin	*Phenobarbital*
Nifedipine	*Phenytoin*
Simvastatin	*Rifampin*
Verapamil	

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Figure 1.18 Some representative cytochrome P450 isozymes.CYP = cytochrome P. *Unlike most other CYP450 enzymes, CYP2D6 is not very susceptible to enzyme induction.

[5] CYP inhibitors: Inhibition of drug metabolism can lead to significant increases in plasma drug concentration and resultant adverse effects or drug toxicity. The most common form of inhibition is through competition for the same isozyme. Some drugs, however, are capable of inhibiting reactions for which they are not substrates (for example, *ketoconazole*), leading to drug interactions. Numerous drugs inhibit one or more of the CYP-dependent biotransformation pathways of the anticoagulant *warfarin*. For example, *omeprazole* is a potent inhibitor of three CYP isozymes involved in *warfarin* metabolism. When taken with *omeprazole*, plasma concentrations of *warfarin* increase, which leads to greater anticoagulant effect and increased risk of bleeding. [Note: The more important CYP inhibitors are *clarithromycin*, *ketoconazole*, and *ritonavir*, because they each inhibit several CYP isozymes.]

b. Phase I reactions not involving the P450 system: These include amine oxidation (for example, oxidation of catecholamines or histamine), alcohol dehydrogenation (for example, *ethanol* oxidation), esterases (for example, metabolism of *aspirin* in the liver), and hydrolysis (for example, *methylphenidate*).

2. Phase II: This phase consists of conjugation reactions. If the metabolite from phase I is sufficiently polar, it can be excreted by the kidneys. However, many phase I metabolites are still too lipophilic to be excreted. A subsequent conjugation reaction with an endogenous substrate, such as glucuronic acid, sulfuric acid, acetic acid, or an amino acid, results in

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polar, usually more water-soluble compounds that are often therapeutically inactive. A notable exception is *morphine-6-glucuronide*, which is more potent than *morphine.* Glucuronidation is the most common and the most important conjugation reaction. [Note: Drugs already possessing an –OH, $–NH_2$, or –COOH group may enter phase II directly and become conjugated without prior phase I metabolism (Figure 1.16).] The highly polar drug conjugates are then excreted by the kidney or in bile.

VI. DRUG CLEARANCE BY THE KIDNEY

Drugs must be sufficiently polar to be eliminated from the body. Removal of drugs from the body occurs via a number of routes; the most important is elimination through the kidney into the urine. Patients with renal dysfunction may be unable to excrete drugs and are at risk for drug accumulation and adverse effects.

A. Renal elimination of a drug

A drug passes through several processes in the kidney before elimination: glomerular filtration, active tubular secretion, and passive tubular reabsorption.

1.Glomerular filtration: Drugs enter the kidney through renal arteries, which divide to form a glomerular capillary plexus. Free drug (not bound to albumin) flows through the capillary slits into the Bowman space as part of the glomerular filtrate (Figure 1.19). The glomerular filtration rate (GFR) is normally about 120 mL/min/1.73 m^2 but may diminish significantly in renal disease. Lipid solubility and pH do not influence the passage of drugs into the glomerular filtrate. However, variations in GFR and protein binding of drugs do affect this process.

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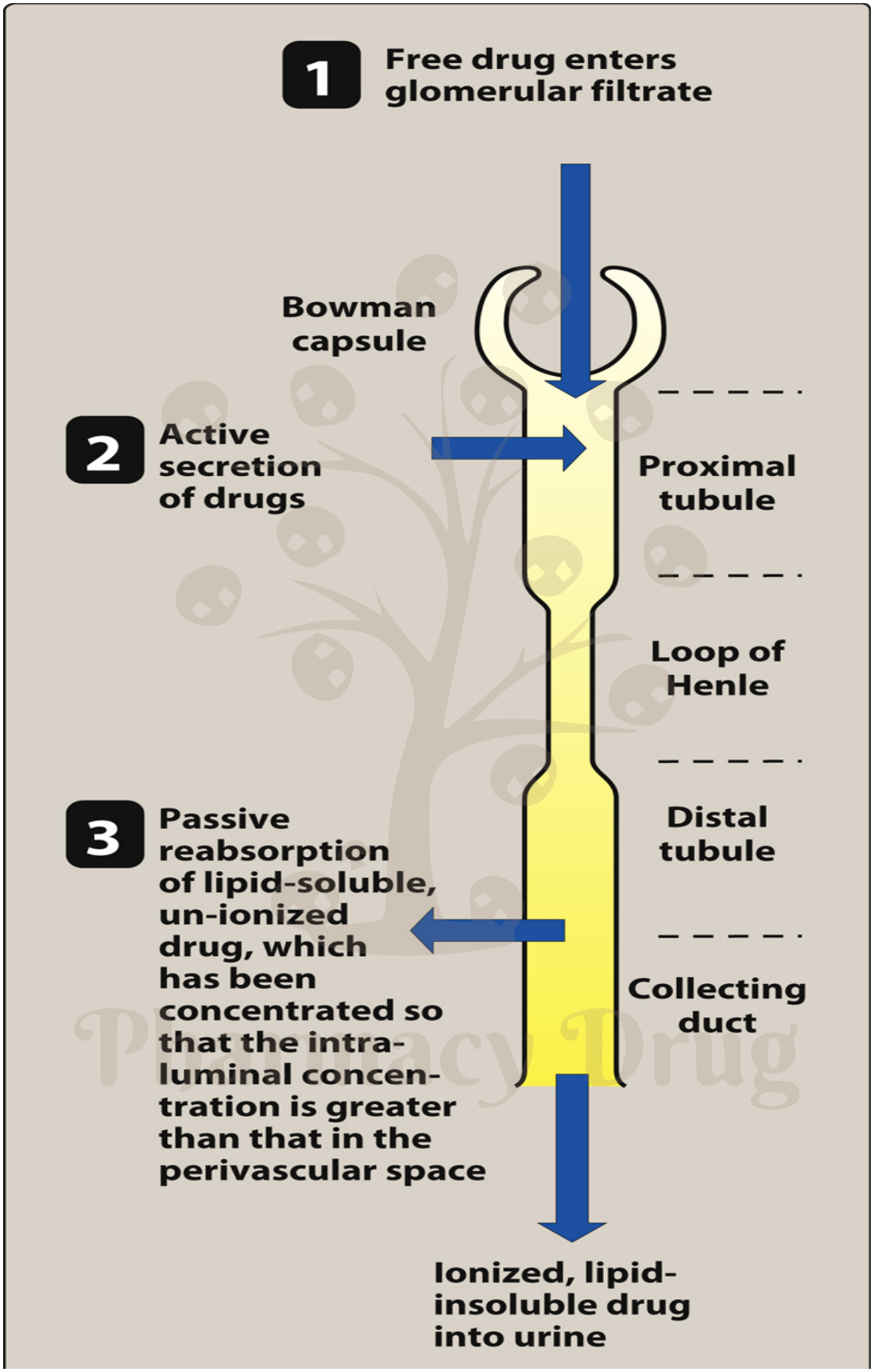

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Figure 1.19 Drug elimination by the kidney.

2. Proximal tubular secretion: Drugs that were not transferred into the glomerular filtrate leave the glomeruli through efferent arterioles, which divide to form a capillary plexus surrounding the nephric lumen in the proximal tubule. Secretion primarily occurs in the proximal tubules by two energy-requiring active transport systems: one for anions (for example, deprotonated forms of weak acids) and one for cations (for example, protonated forms of weak bases). Each of these transport systems shows low specificity and can transport many compounds. Thus, competition between drugs for these carriers can occur within each transport system. [Note: Premature infants and neonates have an incompletely developed tubular secretory mechanism and, thus, may retain certain drugs in the blood.]

3. Distal tubular reabsorption: As a drug moves toward the distal convoluted tubule, its concentration increases and exceeds that of the perivascular space. The drug, if uncharged, may diffuse out of the nephric lumen, back into the systemic circulation (Figure 1.20). Manipulating the urine pH to increase the fraction of ionized drug in the lumen may be done to minimize the amount of back diffusion and increase the clearance of an undesirable drug. Generally, weak acids can be eliminated by alkalinization of the urine, whereas elimination of weak bases may be increased by acidification of the urine. This process is called “ion trapping.” For example, a patient presenting with *phenobarbital* (weak acid) overdose can be given *bicarbonate*, which alkalinizes the urine and keeps the drug ionized, thereby decreasing its reabsorption.

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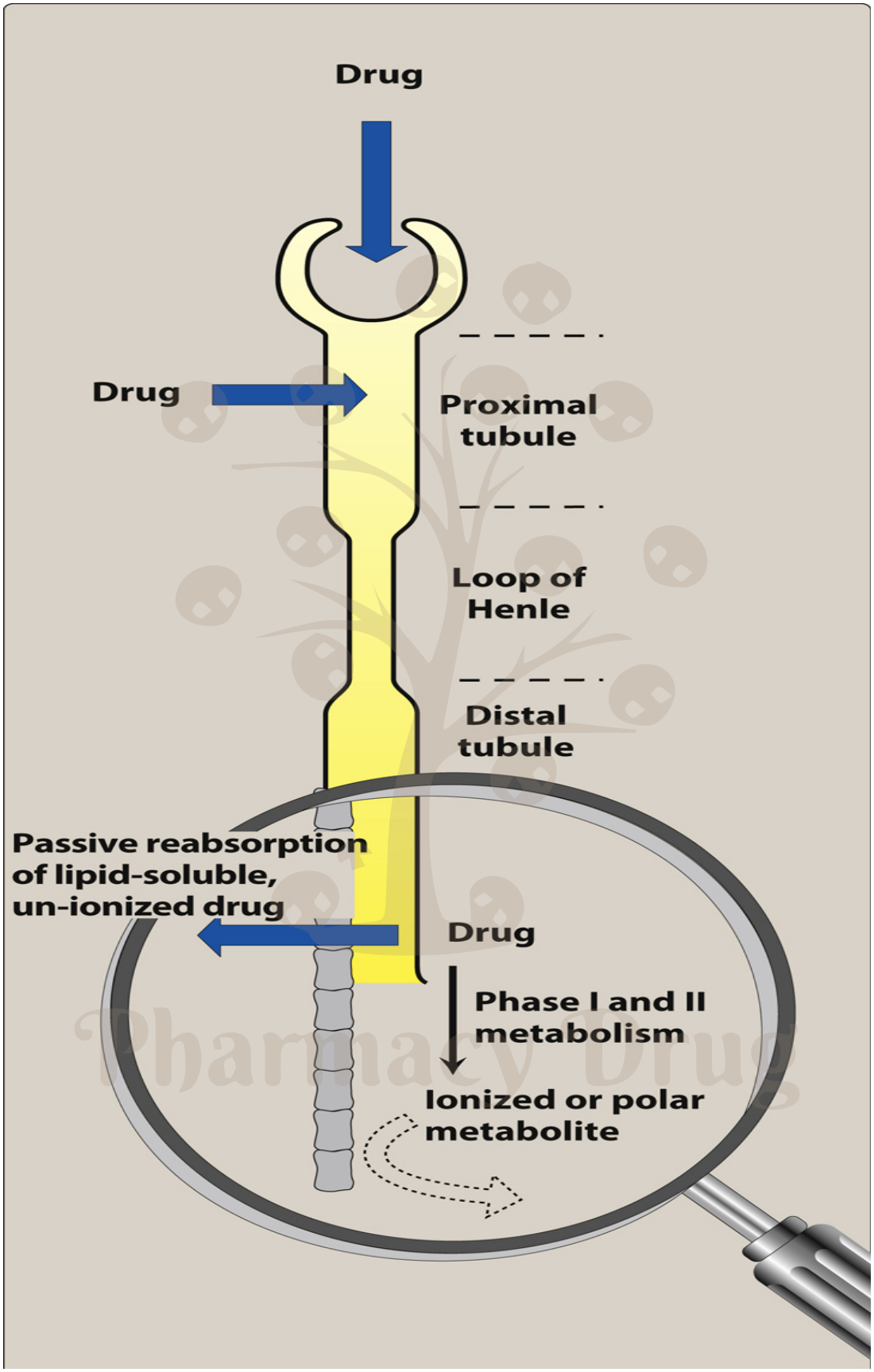

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Figure 1.20 Effect of drug metabolism on reabsorption in the distal tubule.

VII. EXCRETION BY OTHER ROUTES

Drug excretion may also occur via the intestines, bile, lungs, and breast milk, among others. Drugs that are not absorbed after oral administration or drugs that are secreted directly into the intestines or into bile are excreted in the feces. The lungs are primarily involved in the elimination of anesthetic gases (for example, *desflurane*). Elimination of drugs in breast milk may expose the breastfeeding infant to medications and/or metabolites being taken by the mother and is a potential source of undesirable side effects to the infant. Excretion of most drugs into sweat, saliva, tears, hair, and skin occurs only to a small extent. Total body clearance and drug half-life are important measures of drug clearance that are used to optimize drug therapy and minimize toxicity.

A. Total body clearance

The total body (systemic) clearance, CL_{total}, is the sum of all clearances from the drug-metabolizing and drug-eliminating organs. The kidney is often the major organ of excretion. The liver also contributes to drug clearance through metabolism and/or excretion into the bile. Total clearance is calculated using the following equation:

$$CL_{total} = CL_{hepatic} + CL_{renal} + CL_{pulmonary} + CL_{other}$$

where $CL_{hepatic} + CL_{renal}$ are typically the most important.

B. Clinical situations resulting in changes in drug half-life

When a patient has an abnormality that alters the half-life of a drug, adjustment in dosage is required. Patients who may have an

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increase in drug half-life include those with (1) diminished renal or hepatic blood flow, for example, in cardiogenic shock, heart failure, or hemorrhage; (2) decreased ability to extract drug from plasma, for example, in renal disease; and (3) decreased metabolism, for example, when a concomitant drug inhibits metabolism or in hepatic insufficiency, as with cirrhosis. These patients may require a decrease in dosage or less frequent dosing intervals. In contrast, the half-life of a drug may be decreased by increased hepatic blood flow, decreased protein binding, or increased metabolism. This may necessitate higher doses or more frequent dosing intervals.

VIII. DESIGN AND OPTIMIZATION OF DOSAGE REGIMEN

To initiate drug therapy, the clinician must select the appropriate route of administration, dosage, and dosing interval. Selection of a regimen depends on various patient and drug factors, including how rapidly therapeutic levels of a drug must be achieved. Therapy may consist of a single dose of a drug, for example, a sleep-inducing agent, such as *zolpidem.* More commonly, drugs are continually administered, either as an IV infusion or in IV or oral fixed-dose/fixed-time interval regimens (for example, “one tablet every 4 hours”). Continuous or repeated administration results in accumulation of the drug until a steady state occurs. Steady-state concentration is reached when the rate of drug elimination is equal to the rate of drug administration, such that plasma and tissue levels remain relatively constant.

A. Continuous infusion regimens

With continuous IV infusion, the rate of drug entry into the body is constant. Most drugs exhibit first-order elimination, that is, a constant fraction of the drug is cleared per unit of time. Therefore,

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the rate of drug elimination increases proportionately as the plasma concentration increases.

1.Plasma concentration of a drug following continuous iv infusion: Following initiation of a continuous IV infusion, the plasma concentration of a drug rises until a steady state (rate of drug elimination equals rate of drug administration) is reached, at which point the plasma concentration of the drug remains constant.

a. Influence of infusion rate on steady-state concentration: The steady-state plasma concentration (C_{ss}) is directly proportional to the infusion rate. For example, if the infusion rate is doubled, the C_{ss} is doubled (Figure 1.21). Furthermore, the C_{ss} is inversely proportional to the clearance of the drug. Thus, any factor that decreases clearance, such as liver or kidney disease, increases the C_{ss} of an infused drug (assuming V_d remains constant). Factors that increase clearance, such as increased metabolism, decrease the C_{ss}.

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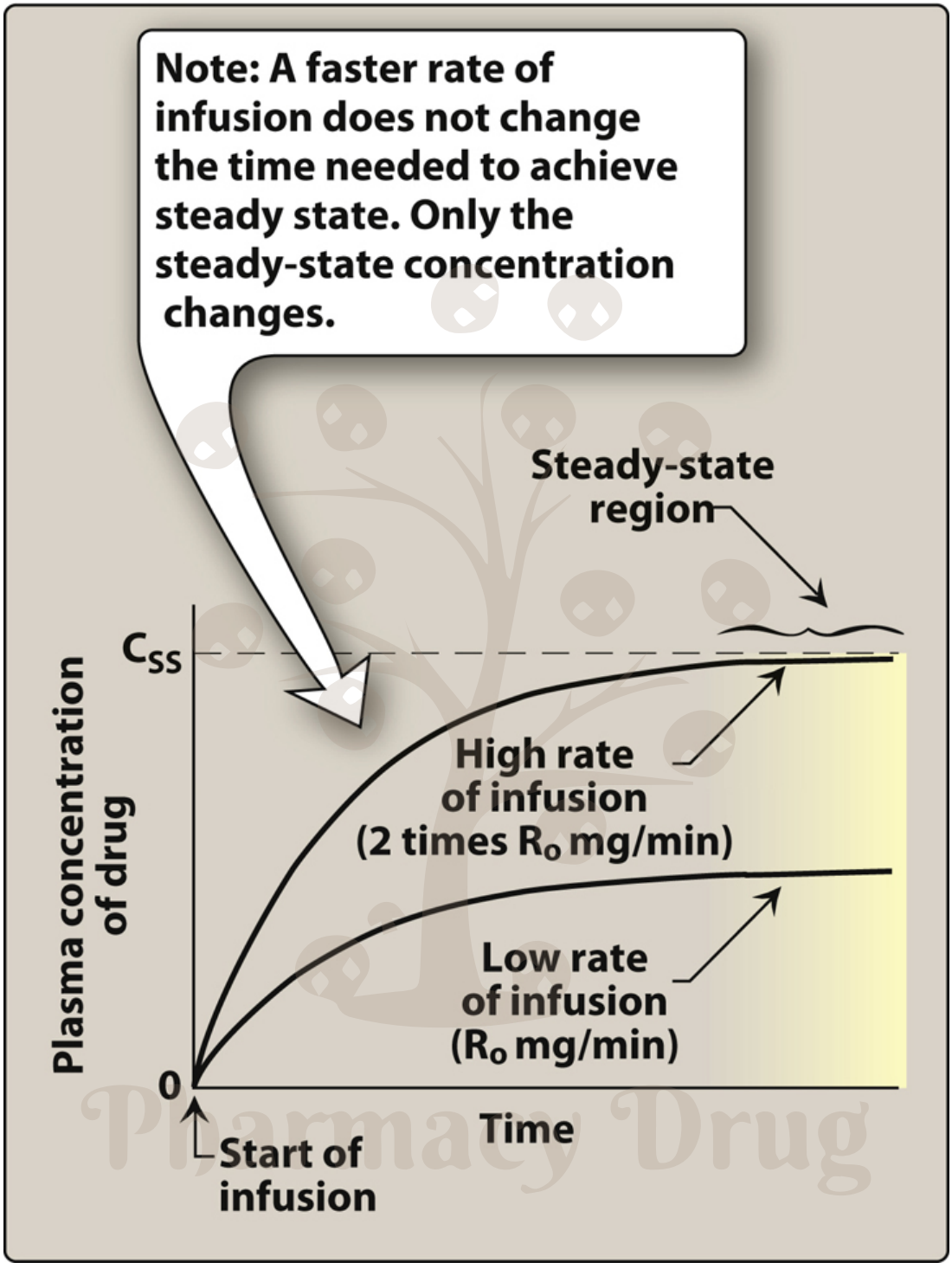

Figure 1.21 Effect of infusion rate on the steady-state concentration of drug in the plasma.C_{ss} = steady-state concentration; R_o = rate of drug

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infusion.Modified from H. P.Range and M. M.Dale . *Pharmacology*. Churchill Livingstone (1987), with permission from Elsevier.

b. Time to reach steady-state drug concentration: The concentration of a drug rises from zero at the start of the infusion to its ultimate steady-state level, C_{ss} (Figure 1.21). The rate constant for attainment of steady state is the rate constant for total body elimination of the drug. Thus, 50% of C_{ss} of a drug is observed after the time elapsed, since the infusion, t, is equal to $t_{1/2}$, where $t_{1/2}$ (or half-life) is the time required for the drug concentration to change by 50%. After another half-life, the drug concentration approaches 75% of C_{ss} (Figure 1.22). The drug concentration is 87.5% of C_{ss} at 3 half-lives and 90% at 3.3 half-lives. Thus, a drug reaches steady state in about 4 to 5 half-lives.

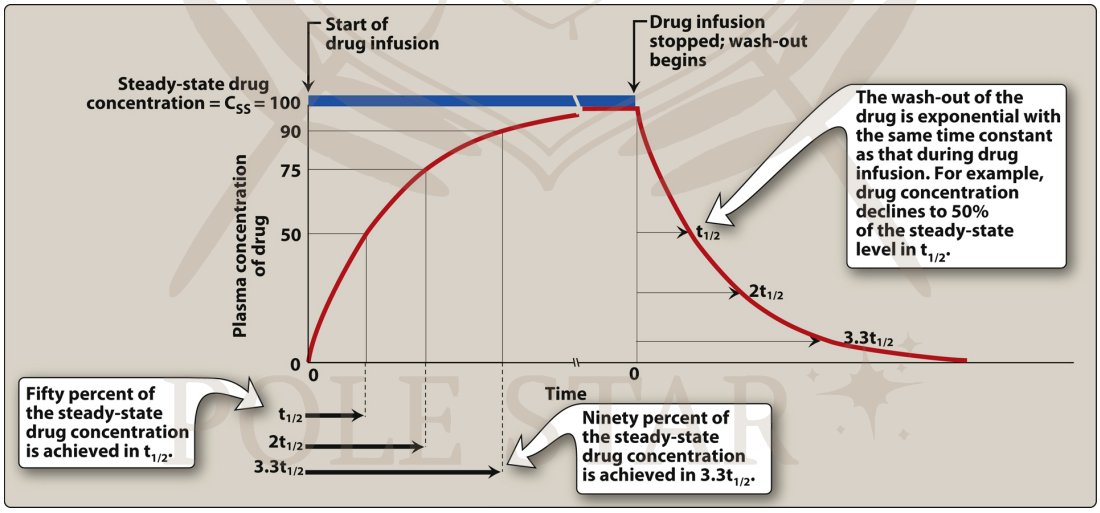

Figure 1.22 Rate of attainment of steady-state concentration of a drug in the plasma after intravenous infusion.

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The sole determinant of the rate that a drug achieves steady state is the half-life ($t_{1/2}$) of the drug, and this rate is influenced only by factors that affect half-life. The rate of approach to steady state is not affected by the rate of infusion. When the infusion is stopped, the plasma concentration of a drug declines (washes out) to zero with the same time course observed in approaching steady state (Figure 1.22).

B. Fixed-dose/Fixed-time regimens

Administration of a drug by fixed doses rather than by continuous infusion is often more convenient. However, fixed doses of IV or oral medications given at fixed intervals result in time-dependent fluctuations in the circulating level of drug, which contrasts with the smooth ascent of drug concentration with continuous infusion.

1. Multiple IV injections: When a drug is given repeatedly at regular intervals, the plasma concentration increases until a steady state is reached (Figure 1.23). Because most drugs are given at intervals shorter than 5 half-lives and are eliminated exponentially with time, some drug from the first dose remains in the body when the second dose is administered, some from the second dose remains when the third dose is given, and so forth. Therefore, the drug accumulates until, within the dosing interval, the rate of drug elimination equals the rate of drug administration and a steady state is achieved.

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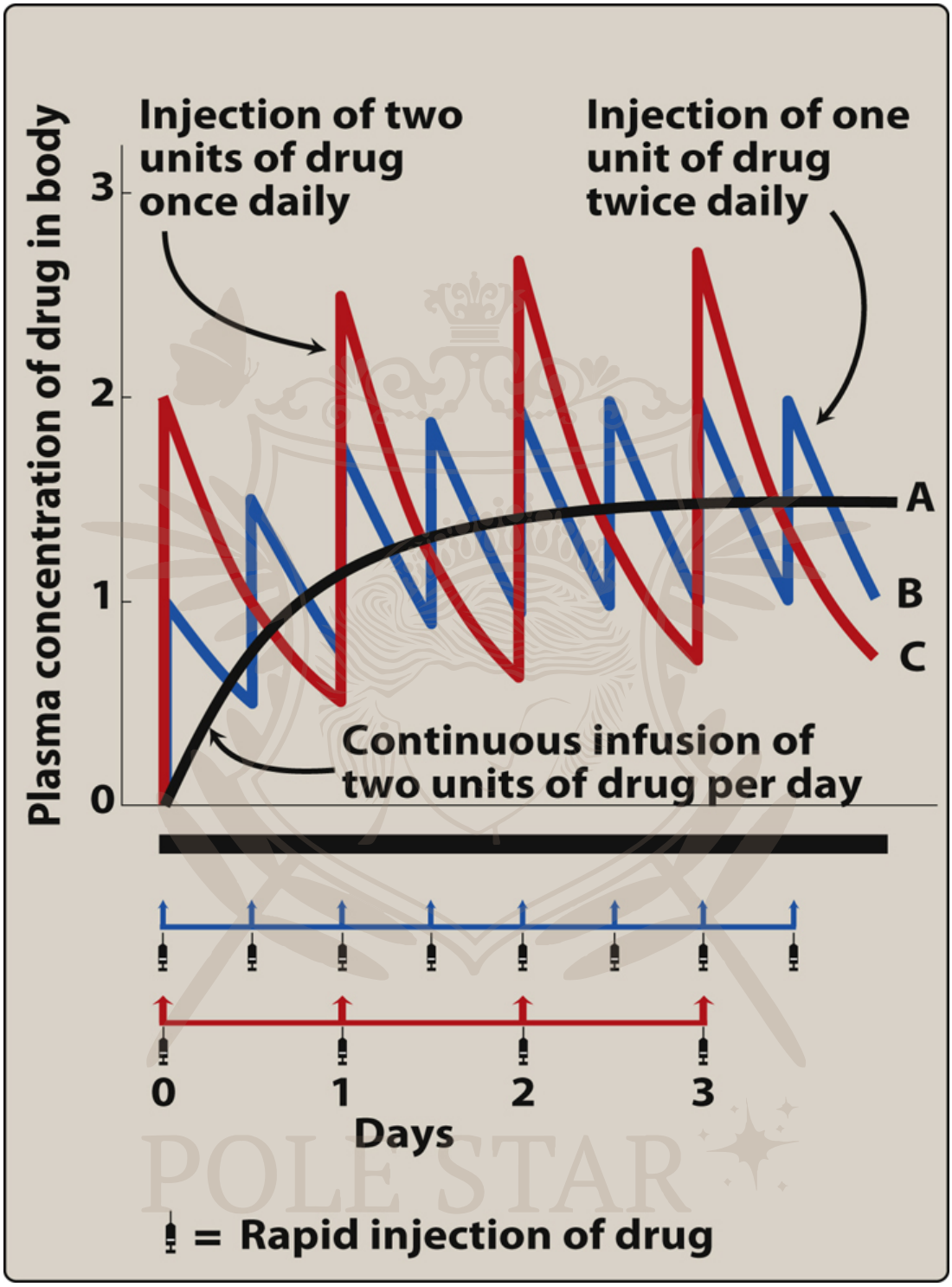

Figure 1.23 Predicted plasma concentrations of a drug given by infusion **(A)**, twice-daily injection **(B)**, or once-daily injection **(C).** Model assumes rapid mixing in a single body compartment and a half-life of 12 hours.Modified from Figure 6.3, Libby . *Braunwald's Heart Disease*: A

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Textbook of Cardiovascular Medicine, 8th ed. Philadelphia, PA, Saunders (2007), with permission from Elsevier.

a. Effect of dosing frequency: With repeated administration at regular intervals, the plasma concentration of a drug oscillates about a mean. Using smaller doses at shorter intervals reduces the amplitude of fluctuations in drug concentration. However, the dosing frequency changes neither the magnitude of C_{ss} nor the rate of achieving C_{ss}.

b. Example of achievement of steady state using different dosage regimens: Curve B of Figure 1.23 shows the amount of drug in the body when 1 unit of a drug is administered IV and repeated at a dosing interval that corresponds to the half-life of the drug. At the end of the first dosing interval, 0.50 units of drug remain from the first dose when the second dose is administered. At the end of the second dosing interval, 0.75 units are present when the third dose is given. The minimal amount of drug remaining during the dosing interval progressively approaches a value of 1.00 unit, whereas the maximal value immediately following drug administration progressively approaches 2.00 units. Therefore, at the steady state, 1.00 unit of drug is lost during the dosing interval, which is exactly matched by the rate of administration. That is, the “rate in” equals the “rate out.” As in the case for IV infusion, 90% of the steady-state value is achieved in 3.3 half-lives.

2. Multiple oral administrations: Most drugs administered on an outpatient basis are oral medications taken at a specific dose one, two, or more times daily. In contrast to IV injection, orally administered drugs may be absorbed slowly, and the plasma concentration of the drug is influenced

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by both the rate of absorption and the rate of elimination (Figure 1.24).

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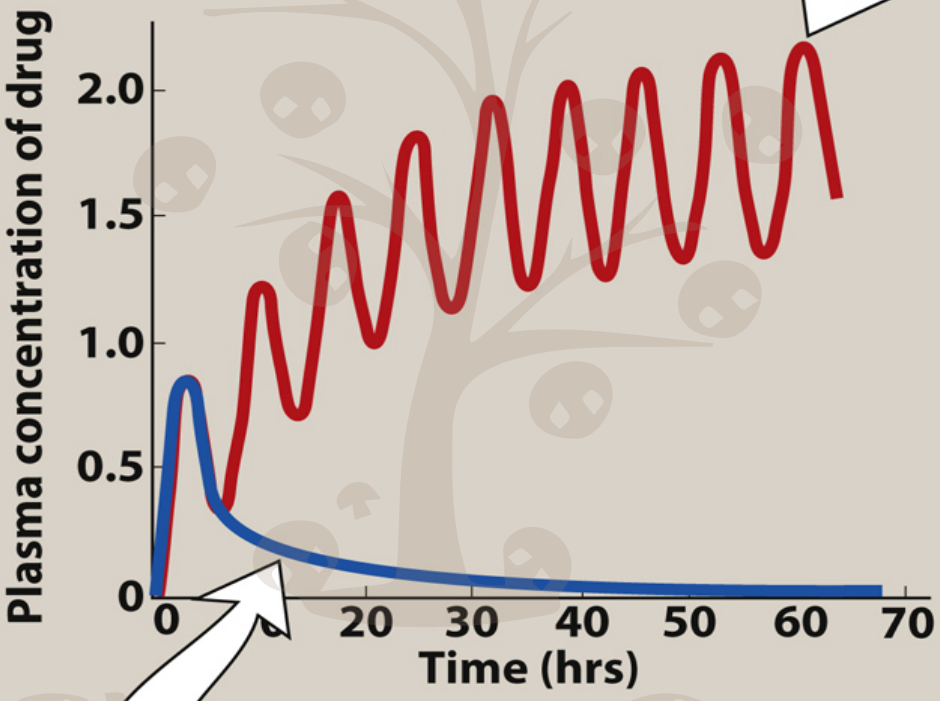
REPEATED FIXED DOSE

Repeated oral administration of a drug results in oscillations in plasma concentrations that are influenced by both the rate of drug absorption and the rate of drug elimination.



Pharmacy Drug

SINGLE FIXED DOSE

A single dose of drug given orally results in a single peak in plasma concentration followed by a continuous decline in drug level.

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Figure 1.24 Predicted plasma concentrations of a drug given by repeated oral administrations.

C. Optimization of dose

The goal of drug therapy is to achieve and maintain concentrations within a therapeutic response window while minimizing toxicity and/or adverse effects. With careful titration, most drugs can achieve this goal. If the therapeutic window (see Chapter 2) of the drug is small (for example, *digoxin* or *lithium*), extra caution should be taken in selecting a dosage regimen, and drug levels should be monitored to ensure attainment of the therapeutic range. Drug regimens are administered as a maintenance dose and may require a loading dose if rapid effects are warranted.

1. Maintenance dose: Drugs are generally administered to maintain a C_{ss} within the therapeutic window. It takes 4 to 5 half-lives for a drug to achieve C_{ss}. To achieve a given concentration, the rate of administration and the rate of elimination of the drug are important. The dosing rate can be determined by knowing the target concentration in plasma (Cp), clearance (CL) of the drug from the systemic circulation, and the fraction (F) absorbed (bioavailability):

$$\text{Dosing rate} = \frac{(\text{Target } C_{plasma})(CL)}{F}$$

2. Loading dose: Sometimes rapid achievement of desired plasma levels is needed (for example, in serious infections or arrhythmias). Therefore, a "loading dose" of drug is administered to achieve the desired plasma level rapidly, followed by a maintenance dose to maintain the steady state (Figure 1.25). In general, the loading dose can be calculated as:

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$$\text{Loading dose} = (V_d) \times (\text{desired steady-state plasma concentration})/F$$

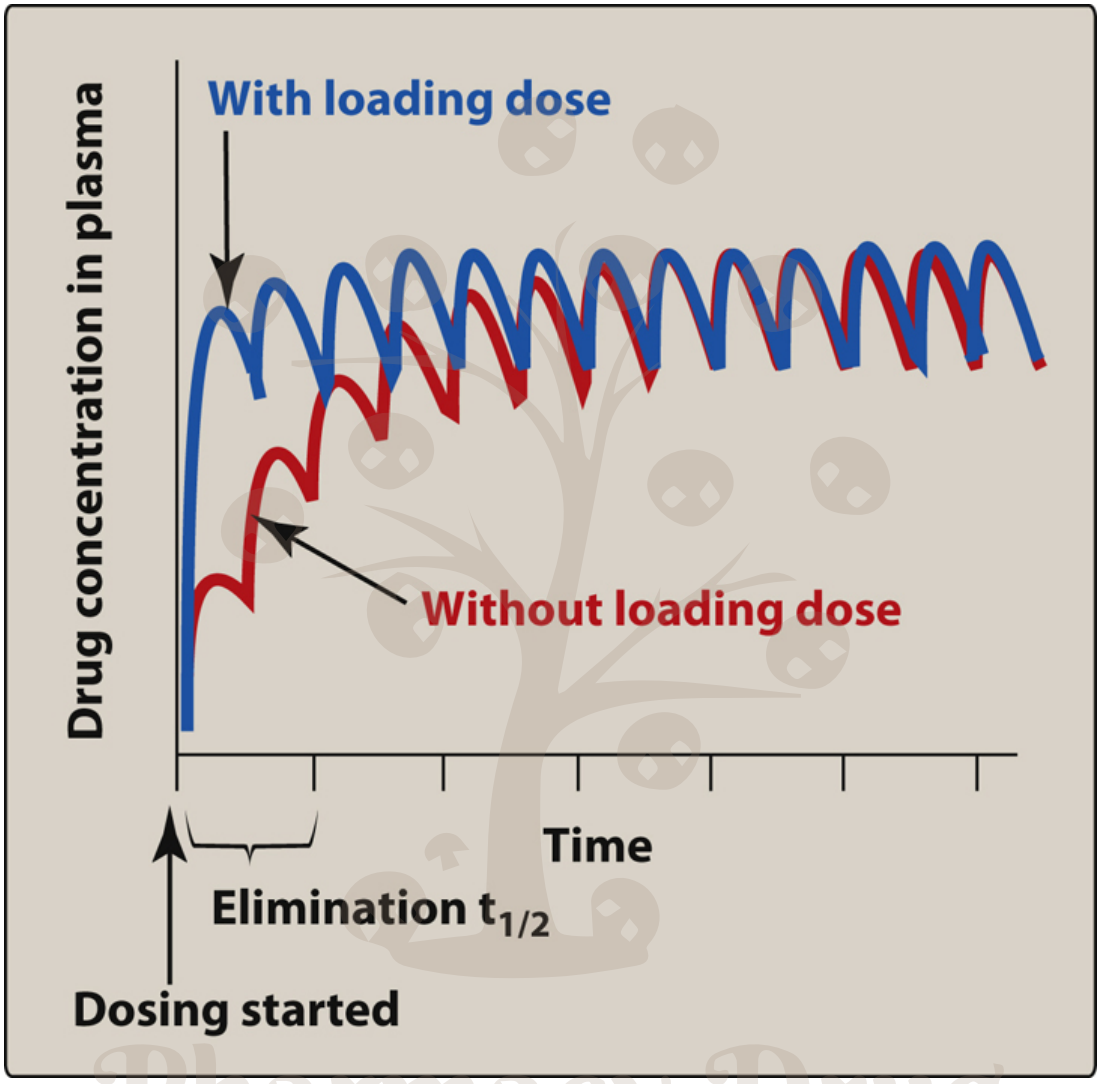

Figure 1.25 Accumulation of drug administered orally without a loading dose and with a single oral loading dose administered at t = 0.

Disadvantages of loading doses include increased risk of drug toxicity and a longer time for the plasma concentration to fall if excess levels occur.

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3.Dose adjustment: The amount of a drug administered for a given condition is estimated based on an "average patient." This approach overlooks interpatient variability in pharmacokinetic parameters such as clearance and V_d, which are quite significant in some cases. Knowledge of pharmacokinetic principles is useful in adjusting dosages to optimize therapy for a given patient. Monitoring drug therapy and correlating it with clinical benefits provides another tool to individualize therapy.

For drugs with a defined therapeutic range, drug concentrations are measured, and the dosage and frequency are adjusted to obtain the desired levels. When determining a dosage adjustment, V_d can be used to calculate the amount of drug needed to achieve a desired plasma concentration. For example, assume a heart failure patient is not well controlled due to inadequate plasma levels of Drug X. Suppose the concentration of Drug X in the plasma is C_1 and the desired target concentration is C_2, a higher concentration. The following calculation can be used to determine how much additional Drug X should be administered to bring the level from C_1 to C_2.

$(V_d)(C_1)$ = Amount of drug initially in the body

$(V_d)(C_2)$ = Amount of drug in the body needed to achieve the desired plasma concentration

The difference between the two values is the additional dosage needed, which equals $V_d\ (C_2 - C_1)$.

Figure 1.26 shows the time course of drug concentration when treatment is started or dosing is changed.

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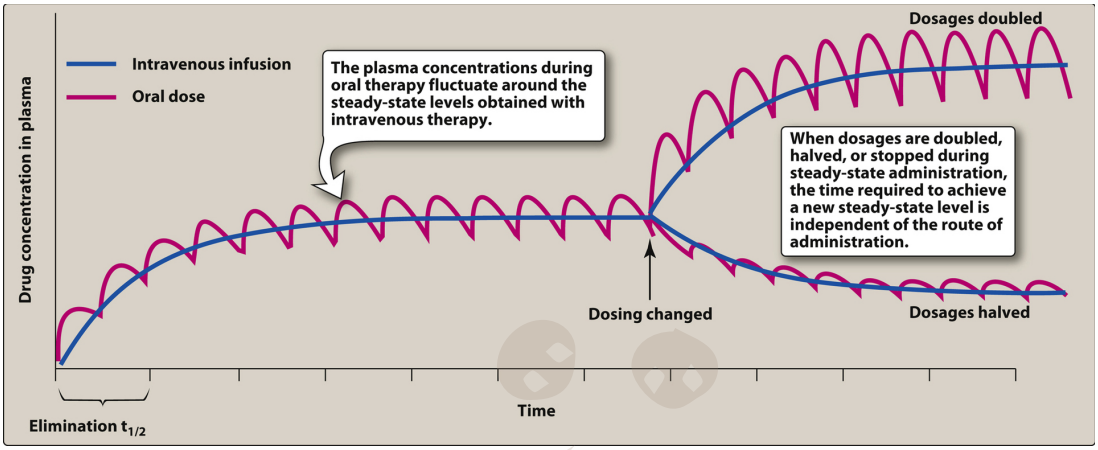

Figure 1.26 Accumulation of drug following sustained administration and following changes in dosing.Oral dosing was at intervals of 50% of $t_{1/2}$.

Chapter Summary

- Pharmacokinetics refers to what the body does to a drug. The pharmacokinetic properties that determine the onset, intensity, and duration of drug actions are: **Absorption, Distribution, Metabolism, and Elimination (ADME)**.
- The mechanisms of absorption of drugs from the gastrointestinal tract are: **passive diffusion, facilitated diffusion, active transport, and endocytosis**.
- P-glycoprotein is a transmembrane transporter protein expressed in various tissues and is involved in the **efflux of drugs** from tissues into the blood, resulting in **reduced bioavailability** and **multidrug resistance**.
- The first-pass metabolism of drugs refers to **rapid metabolism** of a drug in the liver or gut wall when the drug enters the **portal circulation** before entering the systemic circulation.
- Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the **extracellular fluid and tissues**.
- The **apparent volume of distribution, V_d**, is defined as the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma.
- The kidney cannot efficiently excrete lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal convoluted tubules. Therefore, lipid-soluble agents are first metabolized into more polar

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(hydrophilic) substances in the liver via two general sets of reactions, called **phase I** and **phase II**.

- The phase I reactions introduce a polar functional group such as **-OH or -NH $_2$** to convert lipophilic drugs into more **polar molecules.** The phase I reactions are catalyzed by **cytochrome P450 (CYP) enzyme system**.
- Phase II reactions consist of conjugation reactions wherein a phase I metabolite is conjugated with an endogenous substrate such as **glucuronic acid, sulfuric acid, acetic acid, or an amino acid**.
- Patients with renal dysfunction may be unable to excrete drugs and are at risk for **drug accumulation and adverse effects**.
- To initiate drug therapy, the clinician must select the appropriate **route of administration, dosage**, and **dosing interval.** Selection of a regimen depends on various **patient and drug factors**, including how rapidly therapeutic levels of a drug must be achieved.

STUDY QUESTIONS

Choose the ONE best answer.

1.1 An 18-year-old woman is brought to the emergency department due to drug overdose. Which route of administration is the most desirable for administering the antidote for the drug overdose?

A. Intramuscular
B. Intravenous
C. Oral
D. Subcutaneous
E. Transdermal

Correct answer = B. The intravenous route of administration is the most desirable because it results in achievement of therapeutic plasma levels of the antidote rapidly.

1.2 Drug A is a weakly basic drug with a pK_a of 7.8. If administered orally, at which of the following sites of absorption will the drug be able to readily pass through the membrane?

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A. Mouth (pH approximately 7.0)
B. Stomach (pH of 2.5)
C. Duodenum (pH approximately 6.1)
D. Jejunum (pH approximately 8.0)
E. Ileum (pH approximately 7.0)

Correct answer = D. Because Drug A is a weakly basic drug (pK_a = 7.8), it will be predominantly in the nonionized form in the jejunum (pH of 8.0). For weak bases, the nonionized form will permeate through the cell membrane readily.

1.3 KR2250 is an investigational cholesterol-lowering agent. KR2250 has a high molecular weight and is extensively bound to albumin. KR2250 will have a(n) _____ apparent volume of distribution (V_d).

A. High
B. Low
C. Extremely high
D. Normal

Correct answer = B. Because of its high molecular weight and high protein binding, KR2250 will be effectively trapped within the plasma (vascular) compartment and will have a low apparent volume of distribution.

1.4 A 40-year-old man (70 kg) was recently diagnosed with infection involving methicillin-resistant *Staphylococcus aureus.* He received 2000 mg of vancomycin as an IV loading dose. The peak plasma concentration of vancomycin was 28.5 mg/L. The apparent volume of distribution is:

A. 1 L/kg
B. 7 L/kg
C. 10 L/kg
D. 14 L/kg
E. 70 L/kg

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Correct answer = A. V_d = dose/C = 2000 mg/28.5 mg/L = 70.1 L. Because the patient is 70 kg, the apparent volume of distribution in L/kg will be approximately 1 L/kg (70.1 L/70 kg).

1.5 A 55-year-old woman is brought to the emergency department because of seizures. She has a history of renal disease and currently undergoes dialysis. She receives an intravenous infusion of antiseizure Drug X. Which is most likely to be observed with use of Drug X in this patient?

	Half-life	Dosage
A.	↑	↑
B.	↓	↓
C.	↑	↔
D.	↑	↓
E.	↔	↔

A. B. C. D. E. Correct answer = D. Because the patient has a renal disorder, she may not be able to excrete the drug effectively. Therefore, the half-life of Drug X will be prolonged. As the half-life is prolonged, the dosage must be reduced so the patient will not have serious toxic effects of Drug X.

1.6 Ritonavir is coadministered with other anti-HIV drugs to boost their pharmacokinetics. Which property of ritonavir is responsible for improving the pharmacokinetics of other anti-HIV drugs?

A. P-glycoprotein inhibition
B. CYP450 inhibition
C. Urine acidification
D. CYP450 induction

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Correct answer = B. Ritonavir is a potent CYP450 inhibitor. Therefore, it reduces the metabolism of other anti-HIV drugs by CYP450 and increases their plasma levels.

1.7 Which of the following reactions represents phase II of drug metabolism?

A. Amidation
B. Hydrolysis
C. Oxidation
D. Reduction
E. Sulfation

Correct answer = E. Phase II metabolic reactions involve conjugation reactions to make phase I metabolites more polar. Sulfation and glucuronidation are the most common phase II conjugation reactions.

1.8 A pharmacokinetic study of a new antihypertensive drug is being conducted in healthy human volunteers. The half-life of the drug after administration by continuous intravenous infusion is 12 hours. Which of the following best approximates the time for the drug to reach steady state?

A. 24 hours
B. 36 hours
C. 60 hours
D. 120 hours
E. 240 hours

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Correct answer = C. A drug will reach steady state in about 4 to 5 half-lives. Therefore, for this drug with a half-life of 12 hours, the approximate time to reach steady state will be 60 hours.

1.9 A 64-year-old woman (60 kg) is treated with experimental Drug A for type 2 diabetes. Drug A is available as tablets with an oral bioavailability of 90%. If the V_d is 2 L/kg and the desired

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steady-state plasma concentration is 3.0 mg/L, which of the following is the most appropriate oral loading dose of Drug A?

A. 6 mg
B. 6.6 mg
C. 108 mg
D. 360 mg
E. 400 mg

Correct answer = E. For oral dosing, loading dose = [(V_d) × (desired steady-state plasma concentration)/F]. The V_d in this case is corrected to the patient's weight is 120 L. The F value is 0.9 (because bioavailability is 90%, that is, 90/100 = 0.9). Thus, loading dose = (120 L × 3.0 mg/L)/0.9 = 400 mg.

1.10 Valproic acid is a highly protein-bound drug commonly used as an antiepileptic agent. In which disease state should the dose of valproic acid be reduced to avoid adverse events?

A. Bacterial infection
B. Hypoalbuminemia
C. Myocardial infarction
D. Attention deficit hyperactivity disorder

Correct answer = B. Valproic acid is highly bound (90%-95%) to the plasma protein albumin. In hypoalbuminemia (low albumin) patients, the unbound valproic acid concentration will increase, and, therefore, the dose must be reduced to avoid potential adverse events.

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2

Drug–Receptor Interactions and Pharmacodynamics

Joanna Peris

I. OVERVIEW

Pharmacodynamics describes the actions of a drug on the body. Most drugs exert effects, both beneficial and harmful, by interacting with specialized target macromolecules called receptors, which are present on or in the cell. The drug–receptor complex initiates alterations in biochemical and/or molecular activity of a cell by a process called signal transduction (Figure 2.1).

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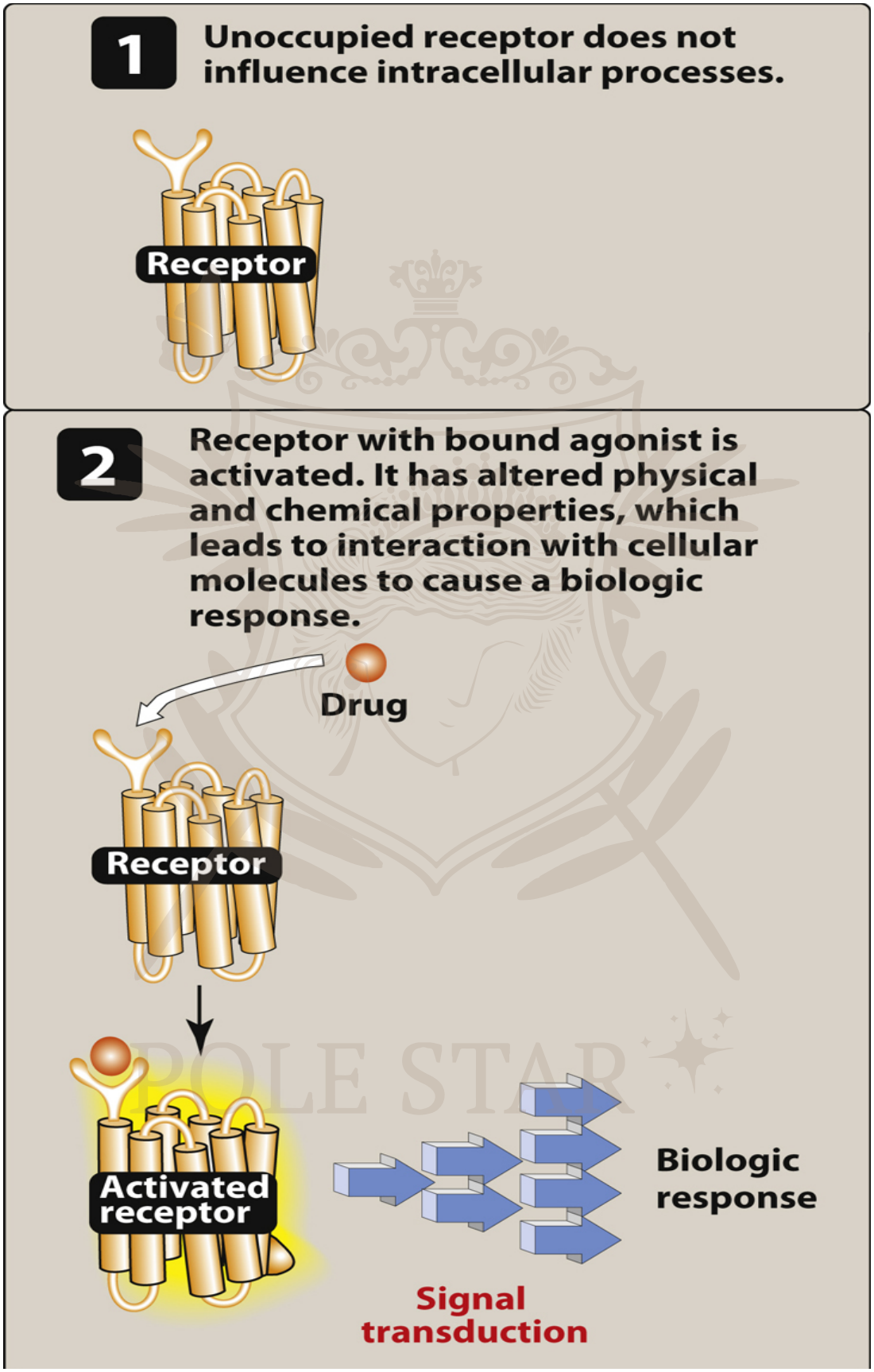
1
Unoccupied receptor does not influence intracellular processes.
Receptor
2
Receptor with bound agonist is activated. It has altered physical and chemical properties, which leads to interaction with cellular molecules to cause a biologic response.
Drug
Receptor
Activated receptor
Biologic response
Signal transduction

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Figure 2.1 The recognition of a drug by a receptor triggers a biologic response.

II. SIGNAL TRANSDUCTION

Drugs act as signals, and receptors act as signal detectors. A drug is termed an "agonist" if it binds to a site on a receptor protein and activates it to initiate a series of reactions that ultimately result in a specific intracellular response. "Second messenger" or effector molecules are part of the cascade of events that translates agonist binding into a cellular response.

A. The drug–receptor complex

Cells have many different types of receptors, each of which is specific for a particular agonist and produces a unique response. Cardiac cell membranes, for example, contain β-adrenergic receptors that bind and respond to epinephrine or norepinephrine. Cardiac cells also contain muscarinic receptors that bind and respond to acetylcholine. These two receptor populations dynamically interact to control the vital functions of the heart.

The magnitude of the cellular response is proportional to the number of drug–receptor complexes. This concept is analogous to the formation of complexes between enzyme and substrate and shares many common features, such as specificity of the receptor for a given agonist. Although much of this chapter centers on the interaction of drugs with specific receptors, it is important to know that not all drugs exert effects by interacting with a receptor. Antacids, for instance, chemically neutralize excess gastric acid, thereby reducing stomach upset.

B. Receptor states

Receptors exist in at least two states, inactive (R) and active (R*), that are in reversible equilibrium with each other, usually favoring the inactive state. Binding of agonists causes the equilibrium to

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shift from R to R* to produce a biologic effect. Antagonists are drugs that bind to the receptor but do not increase the fraction of R*, instead stabilizing the fraction of R. Some drugs (partial agonists) shift the equilibrium from R to R*, but the fraction of R* is less than that caused by an agonist. The magnitude of biological effect is directly related to the fraction of R*. In summary, agonists, antagonists, and partial agonists are examples of molecules or ligands that bind to the activation site on the receptor and can affect the fraction of R*.

C. Major receptor families

A receptor is defined as any biologic molecule to which a drug binds and produces a measurable response. Thus, enzymes, nucleic acids, and structural proteins can act as receptors for drugs or endogenous agonists. However, the richest sources of receptors are membrane-bound proteins that transduce extracellular signals into intracellular responses. These receptors may be divided into four families: (1) ligand-gated ion channels, (2) G protein–coupled receptors, (3) enzyme-linked receptors, and (4) intracellular receptors (Figure 2.2). Generally, hydrophilic ligands interact with receptors that are found on the cell surface (Figure 2.2A-C). In contrast, hydrophobic ligands enter cells through the lipid bilayers of the cell membrane to interact with receptors found inside cells (Figure 2.2D).

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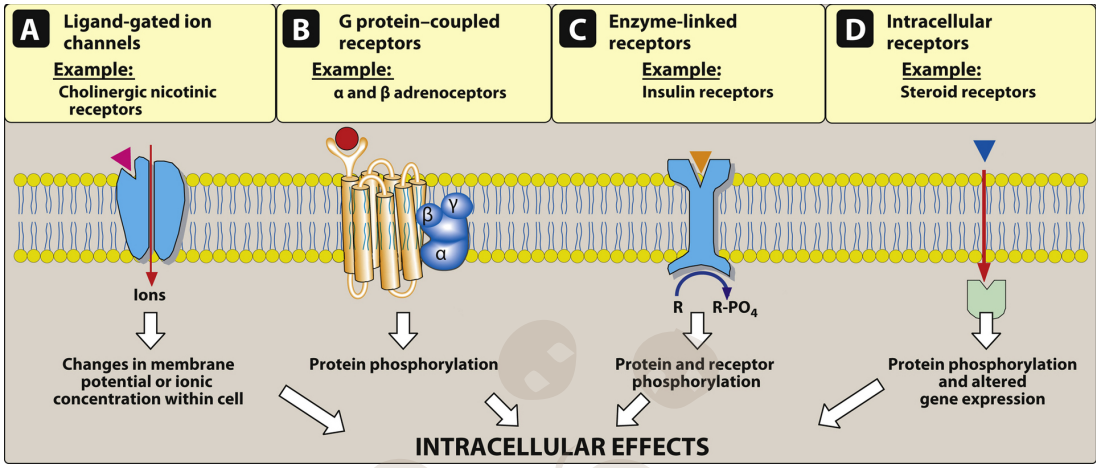

Figure 2.2 Transmembrane signaling mechanisms.**A.** Ligand binds to the extracellular domain of a ligand-gated channel. **B.** Ligand binds to the extracellular domain of a transmembrane receptor, which is coupled to a G protein. **C.** Ligand binds to the extracellular domain of a transmembrane receptor that activates a kinase enzyme. **D.** Lipid-soluble ligand diffuses across the membrane to interact with its intracellular receptor. R = inactive protein.

1.Transmembrane ligand-gated ion channels: The extracellular portion of ligand-gated ion channels contains the drug-binding site. This site regulates the opening of the pore through which ions can flow across cell membranes (Figure 2.2A). The channel is usually closed until the receptor is activated by an agonist, which opens the channel for a few milliseconds. Depending on the ion conducted through these channels, these receptors mediate diverse functions, including neurotransmission and muscle contraction. For example, stimulation of the nicotinic receptor by acetylcholine opens a channel that allows sodium influx and potassium outflux across the cell membranes of neurons or muscle cells. This change in ionic concentrations across the membrane generates an action potential in a neuron and contraction in skeletal and cardiac muscle. On the other hand, agonist stimulation of the A subtype of the γ-aminobutyric acid (GABA) receptor increases chloride influx, resulting in

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hyperpolarization of neurons and less chance of generating an action potential. Drug-binding sites are also found on many voltage-gated ion channels where they can regulate channel function. For example, local anesthetics bind to the voltage-gated sodium channel, inhibiting sodium influx and decreasing neuronal conduction.

2.Transmembrane G protein–coupled receptors: The extracellular portion of this receptor contains the ligand-binding site, and the intracellular portion interacts (when activated) with a G protein. There are many kinds of G proteins (for example, G_s, G_i, and G_q), but all types are composed of three protein subunits. The α subunit binds guanosine triphosphate (GTP), and the β and γ subunits anchor the G protein in the cell membrane (Figure 2.3). Binding of an agonist to the receptor increases GTP binding to the α subunit, causing dissociation of the α-GTP complex from the βγ complex. The α and βγ subunits are then free to interact with specific cellular effectors, usually an enzyme or an ion channel, that cause further actions within the cell. These responses usually last several seconds to minutes. Often, the activated effectors produce “second messenger” molecules that further activate other effectors in the cell, causing a signal cascade effect.

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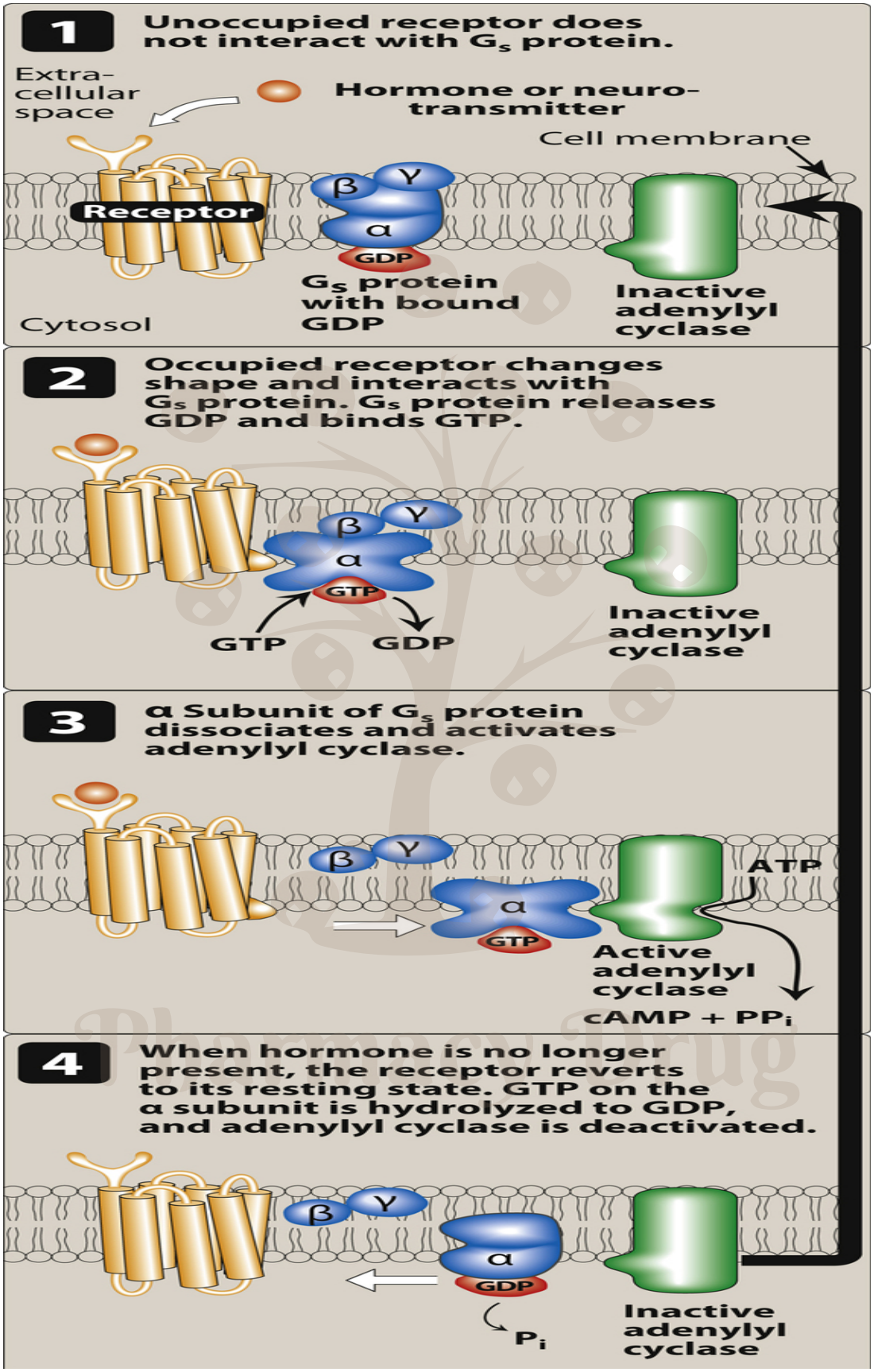

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Figure 2.3 The recognition of chemical signals by G protein–coupled membrane receptors affects the activity of adenylyl cyclase.PP_i = inorganic pyrophosphate.

A common effector, activated by G_s and inhibited by G_i, is adenylyl cyclase, which produces the second messenger cyclic adenosine monophosphate (cAMP). The effector phospholipase C, when activated by G_q, generates two second messengers: inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). DAG and cAMP activate specific protein kinases within the cell, leading to a myriad of physiological effects. IP_3 increases intracellular calcium concentration, which in turn activates other protein kinases.

3.Enzyme-linked receptors: This family of membrane-bound receptors undergoes conformational changes when activated by a ligand, resulting in increased intracellular enzyme activity (Figure 2.4). This response lasts for minutes to hours. The most common enzyme-linked receptors (for example, growth factors and insulin) possess tyrosine kinase activity. When activated, the receptor phosphorylates tyrosine residues on itself and other specific proteins (Figure 2.4). Phosphorylation can substantially modify the structure of the target protein, thereby acting as a molecular switch. For example, the phosphorylated insulin receptor becomes active and, in turn, phosphorylates other proteins that become active. Thus, enzyme-linked receptors often cause a signal cascade effect like that caused by G protein–coupled receptors.

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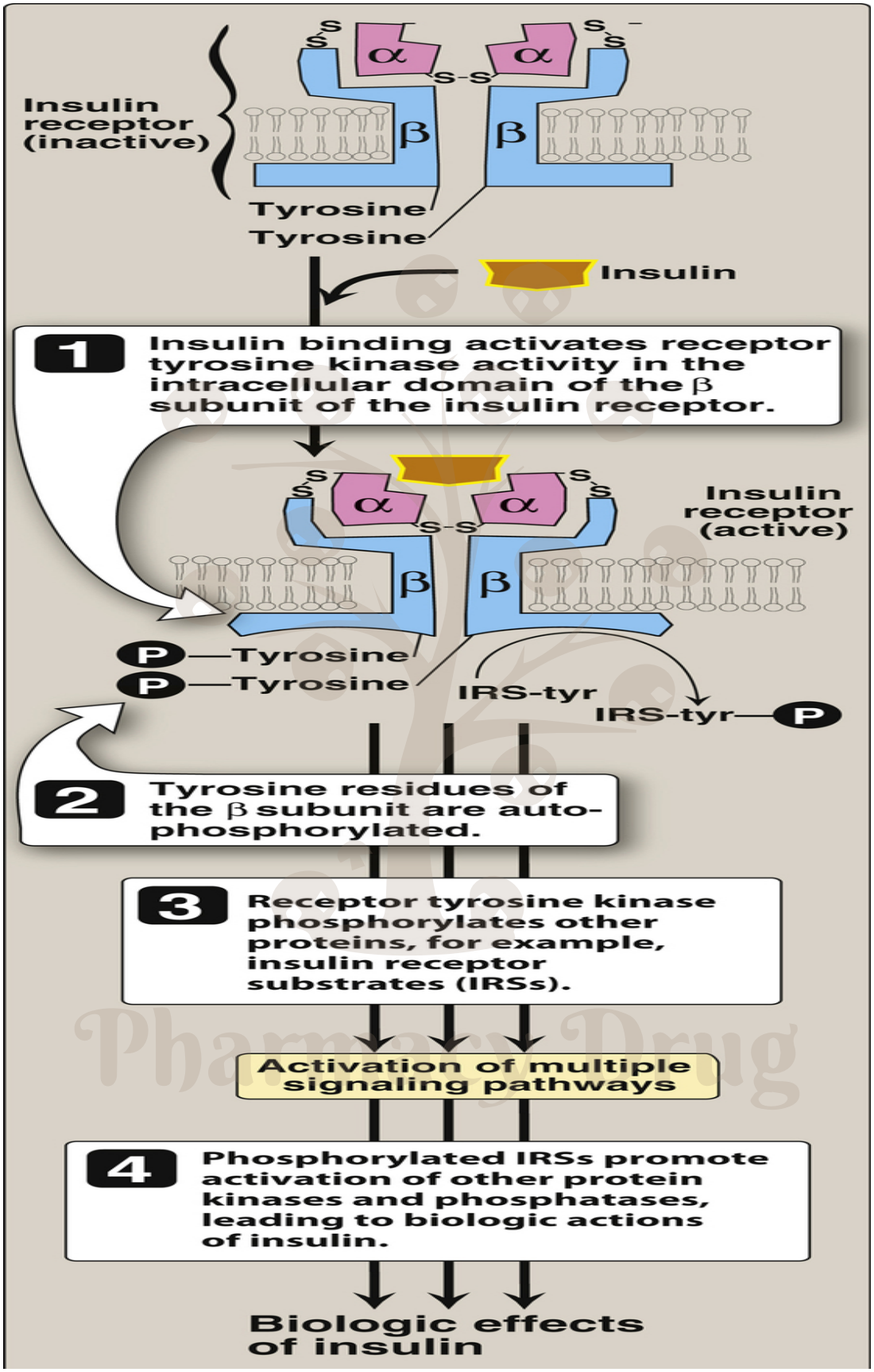

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Figure 2.4 Insulin receptor.

4. Intracellular receptors: The fourth family of receptors differs considerably from the other three in that the receptor is entirely intracellular, and, therefore, the ligand (for example, steroid hormones) must have sufficient lipid solubility to diffuse into the cell to interact with the receptor (Figure 2.5). The primary targets of activated intracellular receptors are transcription factors in the cell nucleus that regulate gene expression. The activation or inactivation of transcription factors alters the transcription of DNA into RNA and subsequently translation of RNA into proteins. The effect of drugs or endogenous ligands that activate intracellular receptors takes hours to days to occur. Other targets of intracellular ligands are structural proteins, enzymes, RNA, and ribosomes. For example, tubulin is the target of antineoplastic agents such as *paclitaxel* (see Chapter 37), the enzyme dihydrofolate reductase is the target of antimicrobials such as *trimethoprim* (see Chapter 31), and the 50S subunit of the bacterial ribosome is the target of macrolide antibiotics such as *erythromycin* (see Chapter 30).

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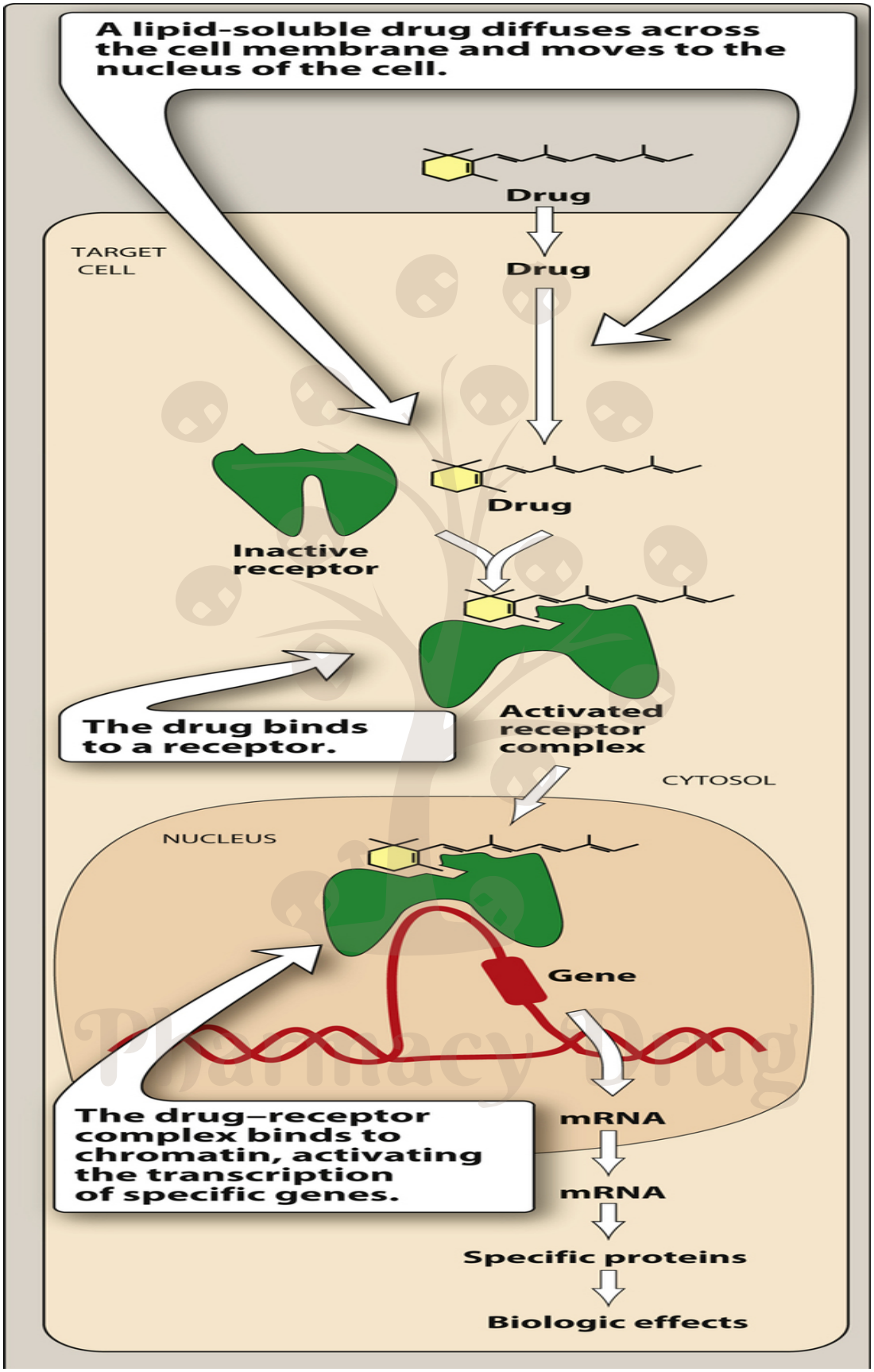

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Figure 2.5 Mechanism of intracellular receptors.mRNA = messenger RNA.

D. Characteristics of signal transduction

Signal transduction has two important features: (1) the ability to amplify small signals and (2) mechanisms to protect the cell from excessive stimulation.

1. **Signal amplification:** A characteristic of G protein–linked and enzyme-linked receptors is the ability to amplify signal intensity and duration via the signal cascade effect. Additionally, activated G proteins persist for a longer duration than does the original agonist–receptor complex. The binding of *albuterol*, for example, may only exist for a few milliseconds, but the subsequent activated G proteins may last for hundreds of milliseconds. Further prolongation and amplification of the initial signal is mediated by the interaction between G proteins and their respective intracellular targets. Because of this amplification, only a fraction of the total receptors for a specific ligand may need to be occupied to elicit a maximal response. Systems that exhibit this behavior are said to have spare receptors. About 99% of insulin receptors are "spare," providing an immense functional reserve that ensures adequate amounts of glucose enter the cell, even if only a small fraction of receptors is occupied. On the other hand, only about 5% to 10% of the total β-adrenoceptors in the heart are spare. Therefore, little functional reserve exists in the failing heart, because most receptors must be occupied to obtain maximum contractility.

2. **Desensitization and downregulation of receptors:** Repeated or continuous administration of an agonist or antagonist often leads to changes in the responsiveness of the receptor. The receptor may become desensitized due to too much agonist stimulation (Figure 2.6), resulting in a diminished response. This phenomenon, called

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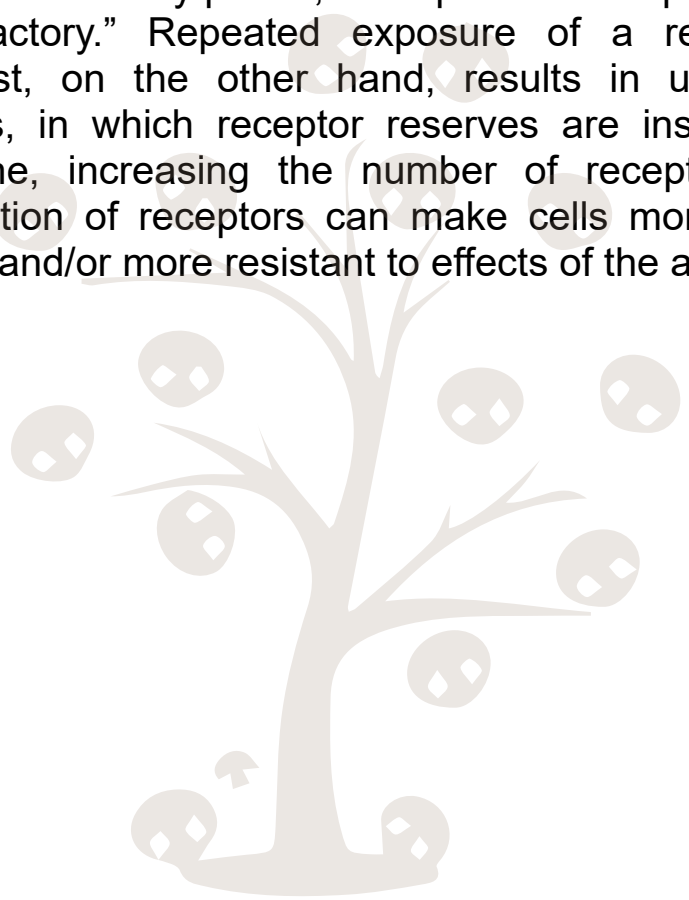
tachyphylaxis, is often due to phosphorylation that renders receptors unresponsive to the agonist. In addition, receptors may be internalized within the cell, making them unavailable for further agonist interaction (downregulation). Some receptors, particularly ion channels, require a finite time following stimulation before they can be activated again. During this recovery phase, unresponsive receptors are said to be “refractory.” Repeated exposure of a receptor to an antagonist, on the other hand, results in upregulation of receptors, in which receptor reserves are inserted into the membrane, increasing the number of receptors available. Upregulation of receptors can make cells more sensitive to agonists and/or more resistant to effects of the antagonist.



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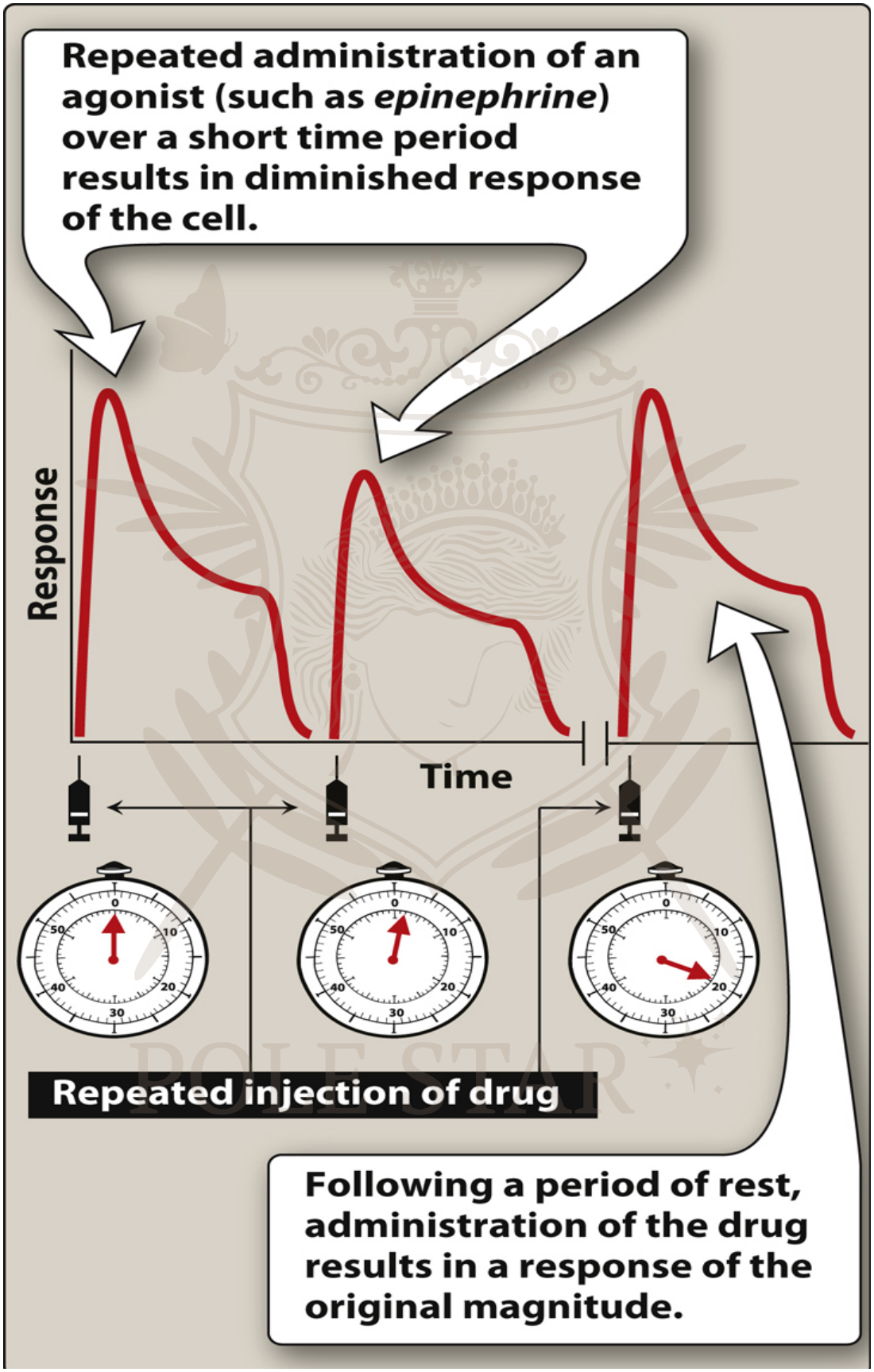
Repeated administration of an agonist (such as *epinephrine*) over a short time period results in diminished response of the cell.
Response
Time
Repeated injection of drug
Following a period of rest, administration of the drug results in a response of the original magnitude.

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Figure 2.6 Desensitization of receptors.

Clinical Application 2.1: Downregulation of Receptors

Overstimulation of receptors with agonist often results in receptor downregulation and decreased efficacy of a drug. For example, a patient may experience adequate analgesic response with an initial dose of *morphine* for back pain; however, after repeated use of this opioid medication the patient may find they no longer experience the same pain relief and have developed tolerance to the regimen. The mechanism of this drug tolerance is a decrease in the number and responsiveness of opioid receptors to which *morphine* binds, thereby requiring a higher dose of *morphine* to cause the same cellular signal that ultimately results in pain relief.

III. DOSE–RESPONSE RELATIONSHIPS

Agonist drugs mimic the action of the endogenous ligand for the receptor (for example, *isoproterenol* mimics norepinephrine on β_1 receptors of the heart). The magnitude of the drug effect depends on receptor sensitivity to the drug and the drug concentration at the receptor site, which, in turn, is determined by both the dose of drug administered and by the drug's pharmacokinetic profile, such as rate of absorption, distribution, metabolism, and elimination.

A. Graded dose–response relationship

As the concentration of a drug increases, its pharmacologic effect also gradually increases until all the receptors are occupied (the maximum effect). Plotting the magnitude of response against increasing doses of a drug produces a graded dose–response curve that has the general shape depicted in Figure 2.7A. Two important drug characteristics, potency and efficacy, can be determined by graded dose–response curves.

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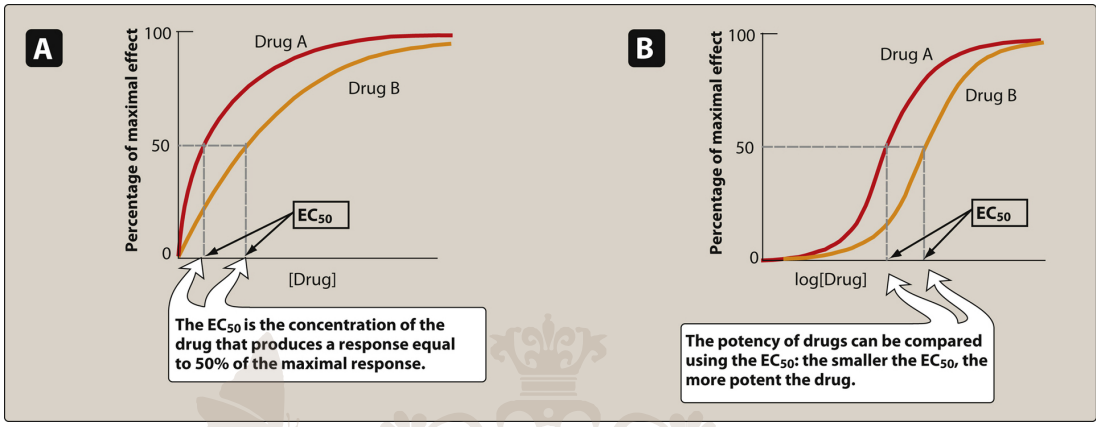

Figure 2.7 The effect of dose on the magnitude of pharmacologic response.**Panel A** is a linear plot. **Panel B** is a semilogarithmic plot of the same data. EC_{50} = drug dose causing 50% of maximal response.

1.Potency: Potency is a measure of the amount of drug necessary to produce an effect. The concentration of drug producing 50% of the maximum effect (EC_{50}) is often used to determine potency. In Figure 2.7, the EC_{50} for Drugs A and B indicate that Drug A is more potent than Drug B, because a lesser amount of Drug A is needed to obtain 50% effect. Therapeutic preparations of drugs reflect their potency. For example, *candesartan* and *irbesartan* are angiotensin receptor blockers used to treat hypertension. The therapeutic dose range for *candesartan* is 4 to 32 mg, as compared with 75 to 300 mg for *irbesartan.* Therefore, *candesartan* is more potent than *irbesartan* (it has a lower EC_{50} value). Since the range of drug concentrations that cause from 1% to 99% of maximal response usually spans several orders of magnitude, semilogarithmic plots are used to graph the complete range of doses. As shown in Figure 2.7B, the curves become sigmoidal in shape, which simplifies the interpretation of the dose–response curve.

2.Efficacy: Efficacy is the magnitude of response a drug causes when it interacts with a receptor. Efficacy is dependent on the number of drug–receptor complexes formed and the

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intrinsic activity of the drug (its ability to activate the receptor and cause a cellular response). Maximal efficacy of a drug (E_{max}) assumes that the drug occupies all receptors, and no increase in response is observed in response to higher concentrations of drug. The maximal response differs between full and partial agonists, even when the drug occupies 100% of the receptors. Similarly, even though an antagonist occupies 100% of the receptor sites, no receptor activation results and E_{max} is zero. Efficacy is a more clinically useful characteristic than potency, since a drug with greater efficacy is more therapeutically beneficial than one that is more potent. Figure 2.8 shows the response to drugs of differing potency and efficacy.

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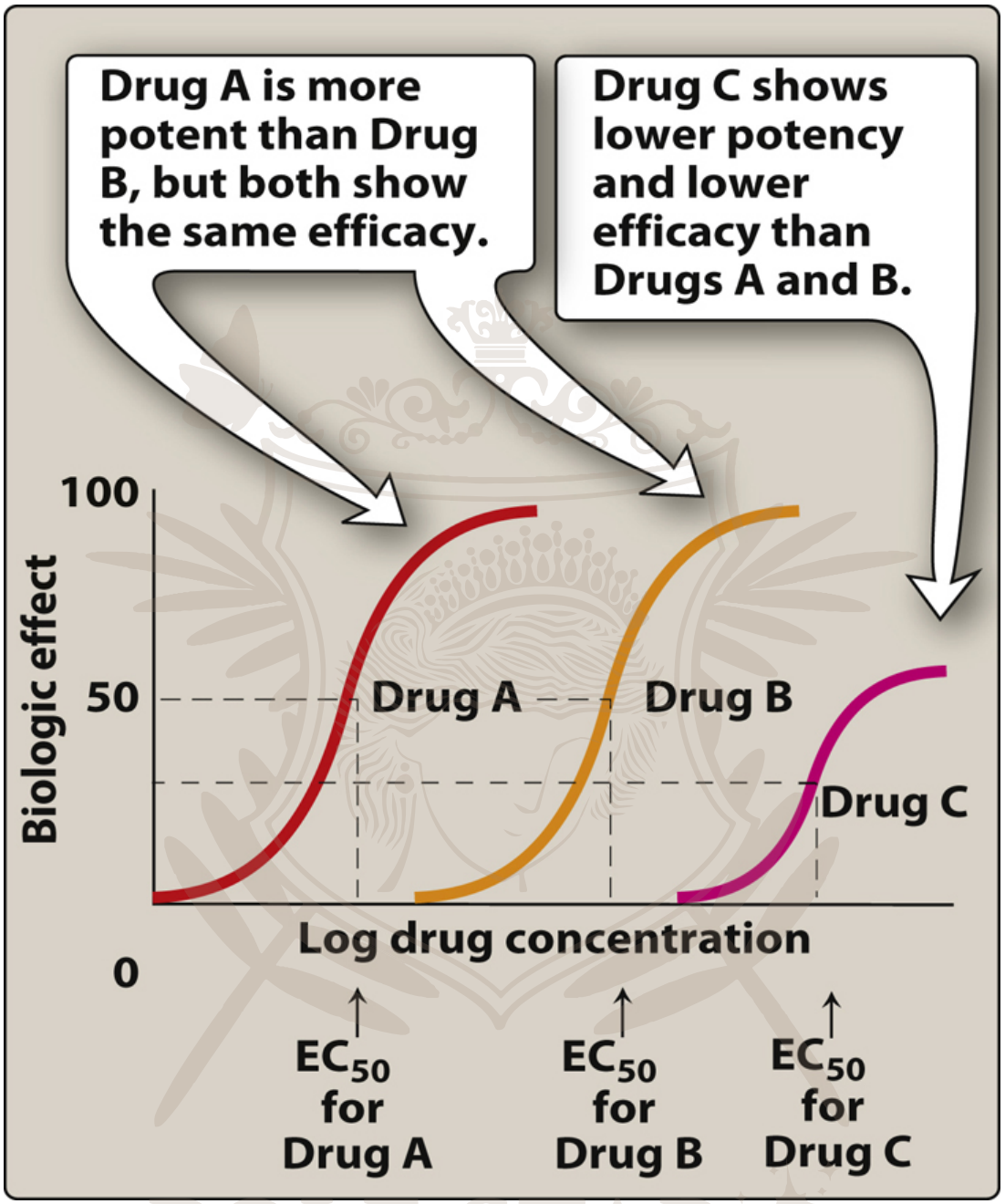

Figure 2.8 Typical dose–response curve for drugs showing differences in potency and efficacy.EC_{50} = drug dose that shows 50% of maximal response.

Clinical Application 2.2: Clinical Relevance of Potency Versus Efficacy of Drugs

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Drugs that have lower potency (for example, *ibuprofen*) require administration of higher doses to achieve the same efficacy as higher potency drugs (for example, *naproxen*). While it might seem that *naproxen* would have better clinical usefulness than *ibuprofen*, since both drugs have the same maximal efficacy at relieving headache and fever, they are therapeutically equivalent. By contrast, an analgesic with greater efficacy than *naproxen* (for example, *morphine*) has greater clinical usefulness, since *morphine* can be used to relieve severe pain (for example, cancer pain) while *naproxen* is less effective.

B. Effect of drug concentration on receptor binding

The quantitative relationship between drug concentration and receptor occupancy applies the law of mass action to the kinetics of the binding of drug and receptor molecules:

$$\text{Drug} + \text{Receptor} \rightleftarrows \text{Drug} - \text{receptor complex} \rightarrow \text{Biologic effect}$$

By assuming that the binding of one drug molecule does not alter the binding of subsequent molecules and applying the law of mass action, we can mathematically express the relationship between the percentage (or fraction) of bound receptors and the drug concentration:

$$\frac{[DR]}{[R_t]} = \frac{[D]}{K_d + [D]} \quad (1)$$

where [D] = the concentration of free drug, [DR] = the concentration of bound drug, $[R_t]$ = the total number of receptors, and K_d = the equilibrium dissociation constant for the drug from the receptor. The value of K_d can be used to determine the affinity of a drug for its receptor. Affinity describes the strength of the interaction (binding) between a ligand and its receptor. The higher the K_d value, the weaker the interaction and the lower the affinity, and vice versa. Eq. 1 defines a curve that has the shapes shown in Figure 2.9 when plotted against drug concentration (panel A) or log drug concentration (panel B). As the concentration of free drug increases, the ratio of the concentrations of bound receptors to

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total receptors approaches unity, thereby producing the maximal effect. Thus, it is not surprising that the curves shown in Figure 2.9 and those representing the relationship between dose and effect (Figure 2.7) are similar.

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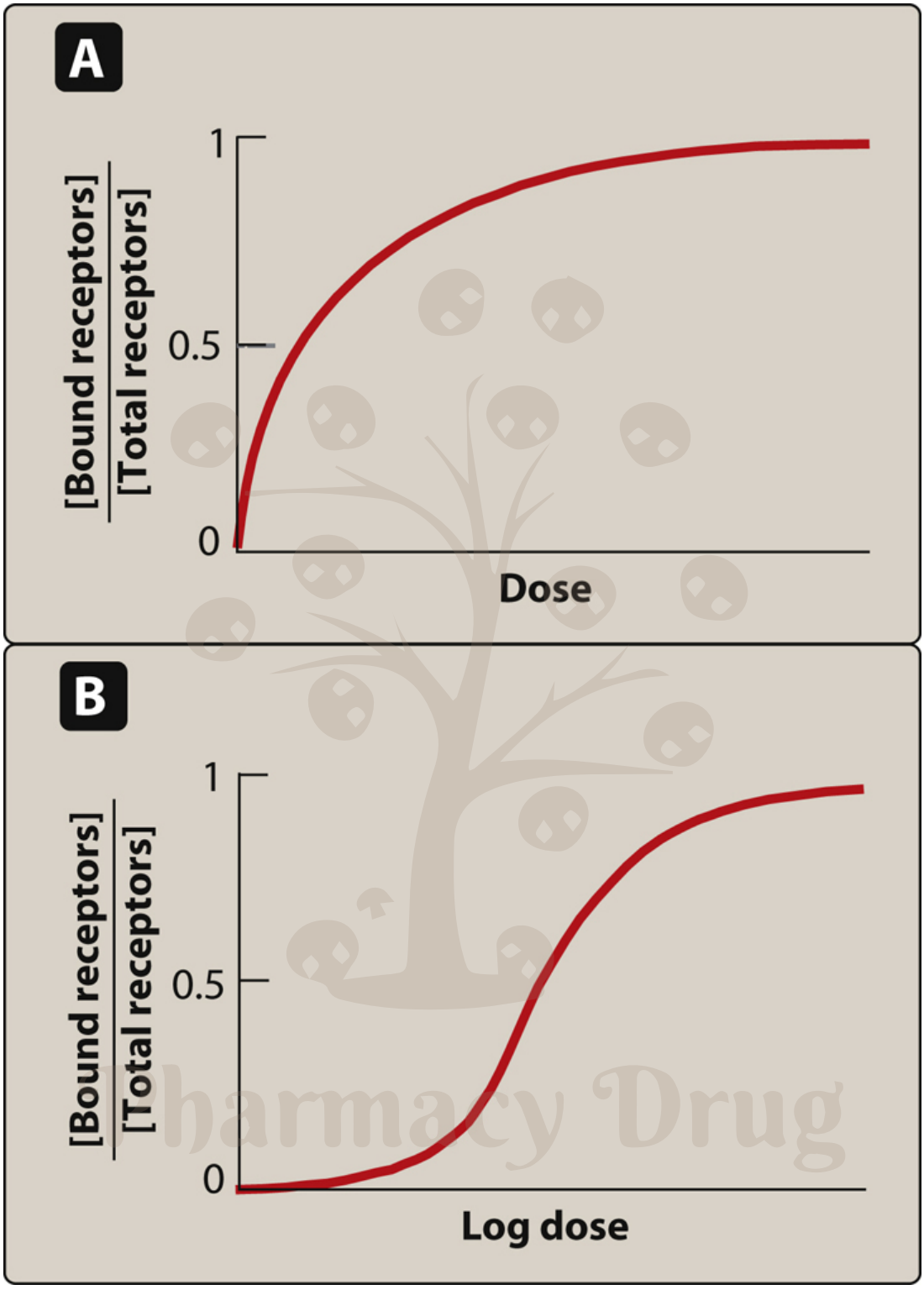

Figure 2.9 The effect of dose on the magnitude of drug binding.**Panel A** is a linear plot. **Panel B** is a semilogarithmic plot of the same data.

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C. Relationship of drug binding to pharmacologic effect

The law of mass action can be applied to drug concentration and response providing the following assumptions are met: (1) the magnitude of the response is proportional to the number of receptors occupied by drug, (2) the E_{max} occurs when all receptors are bound, and (3) one molecule of drug binds to only one molecule of receptor. In this case,

$$\frac{[E]}{[E_{max}]} = \frac{[D]}{K_d + [D]} \quad (2)$$

where [E] = the effect of the drug at concentration [D] and $[E_{max}]$ = the maximal effect of the drug.

Thus, it follows that if a specific population of receptors is vital for mediating a physiological effect, the affinity of an agonist for binding to those receptors should be related to the potency of that drug for causing that physiological effect. Many drugs and most neurotransmitters can bind to more than one type of receptor, thereby causing both desired therapeutic effects and undesired adverse effects. In order to establish a relationship between drug occupation of a particular receptor subtype and the corresponding biological response to that drug, correlation curves of receptor affinity and drug potency are often constructed (Figure 2.10).

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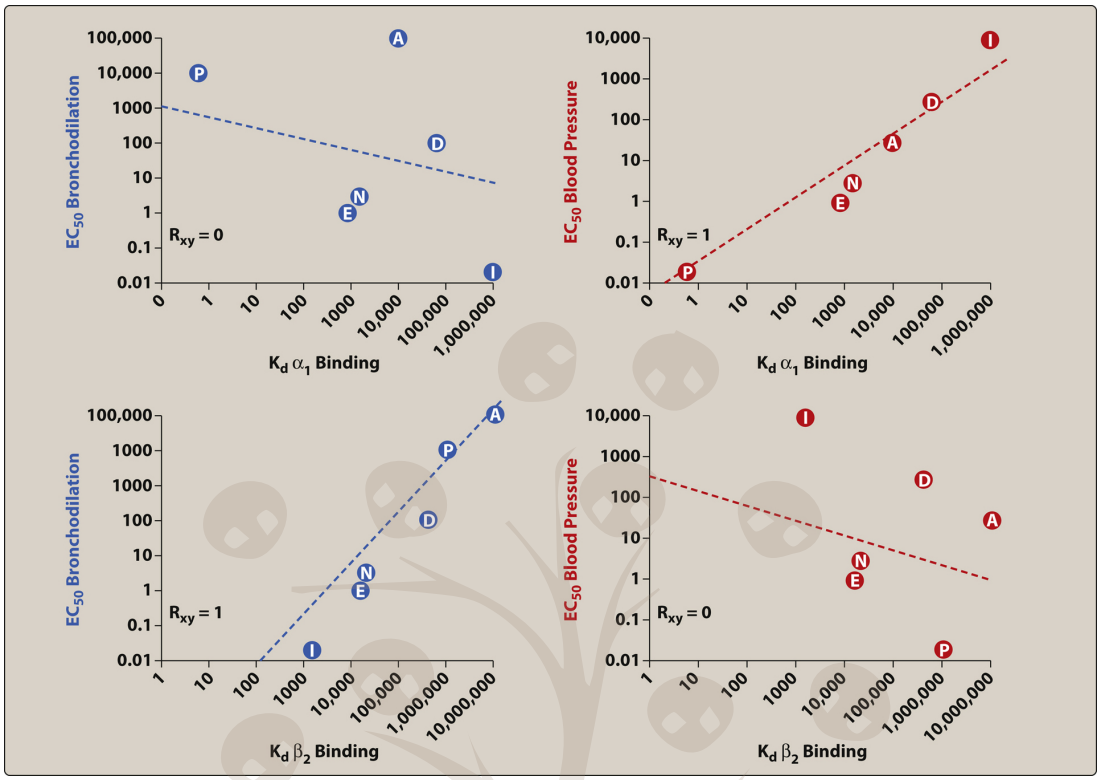

Figure 2.10 Correlation of drug affinity for receptor binding and potency for causing a physiological effect.A positive correlation should exist between the affinity (K_d value) of a drug for binding to a specific receptor subtype and the potency (EC_{50} value) of that drug to cause physiological responses mediated by that receptor population. For example, many drugs have affinity for both α_1 and β_2 adrenergic receptors. The circled letters in the figure represent agonists with varying affinities for α_1 and β_2 receptors. However, from the data provided, it becomes clear that α_1 receptors only mediate changes in blood pressure, while β_2 receptors only mediate changes in bronchodilation.

IV. INTRINSIC ACTIVITY

As mentioned above, an agonist binds to a receptor and produces a biologic response based on the concentration of the agonist, its

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affinity for the receptor, and, hence, the fraction of occupied receptors. However, the intrinsic activity of a drug further determines its ability to fully or partially activate the receptors. Drugs may be categorized according to their intrinsic activity and resulting E_{max} values.

A. Full agonists

If a drug binds to a receptor and produces a maximal biologic response that mimics the response to the endogenous ligand, it is a full agonist (Figure 2.11). Full agonists bind to a receptor, stabilizing the receptor in its active state, and are said to have an intrinsic activity of one. All full agonists for a receptor population should produce the same E_{max}. For example, *phenylephrine* is a full agonist at α_1-adrenoceptors, because it produces the same E_{max} as the endogenous ligand, norepinephrine. Upon binding to α_1-adrenoceptors on vascular smooth muscle, both norepinephrine and *phenylephrine* stabilize the receptor in its active state, thereby increasing G_q activation. Activation of G_q increases intracellular Ca^{2+}, causing interaction of actin and myosin filaments and shortening of the muscle cells. The diameter of the arteriole decreases, causing an increase in resistance to blood flow through the vessel and an increase in blood pressure. Thus, effects of agonists on intracellular molecules, cells, tissues, and intact organisms are all attributable to interaction of the drug with the receptor. For full agonists, the dose–response curves for receptor binding and each of the biological responses should be comparable.

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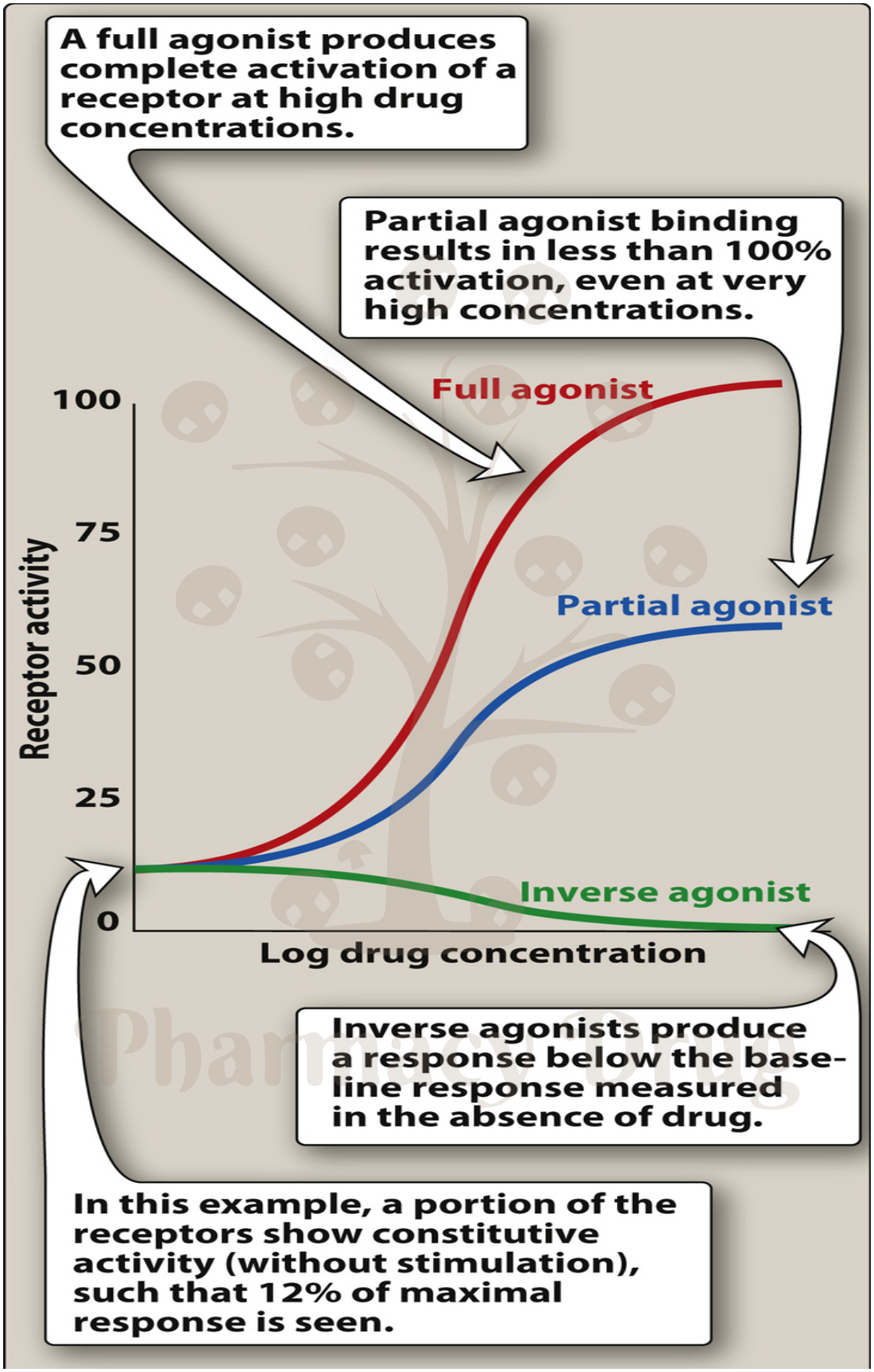

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Figure 2.11 Effects of full agonists, partial agonists, and inverse agonists on receptor activity.

B. Partial agonists

Partial agonists have intrinsic activities greater than zero but less than one (Figure 2.11). Even when all the receptors are occupied, partial agonists cannot produce the same E_{max} as a full agonist. Even so, a partial agonist may have an affinity that is greater than, less than, or equivalent to that of a full agonist. A partial agonist may also act as a partial antagonist of a full agonist (Figure 2.12). As the number of receptors occupied by the partial agonist increases, the number of receptors that can be occupied by the full agonist decreases and therefore E_{max} would decrease until it reached the E_{max} of the partial agonist. This potential of partial agonists to act as both an agonist and antagonist may have therapeutic utility. For example, *aripiprazole*, an atypical antipsychotic, is a partial agonist at selected dopamine receptors. Overactive dopaminergic pathways tend to be inhibited by *aripiprazole*, whereas underactive pathways are stimulated. This might explain the ability of *aripiprazole* to improve symptoms of schizophrenia, with a small risk of causing extrapyramidal adverse effects (see Chapter 18).

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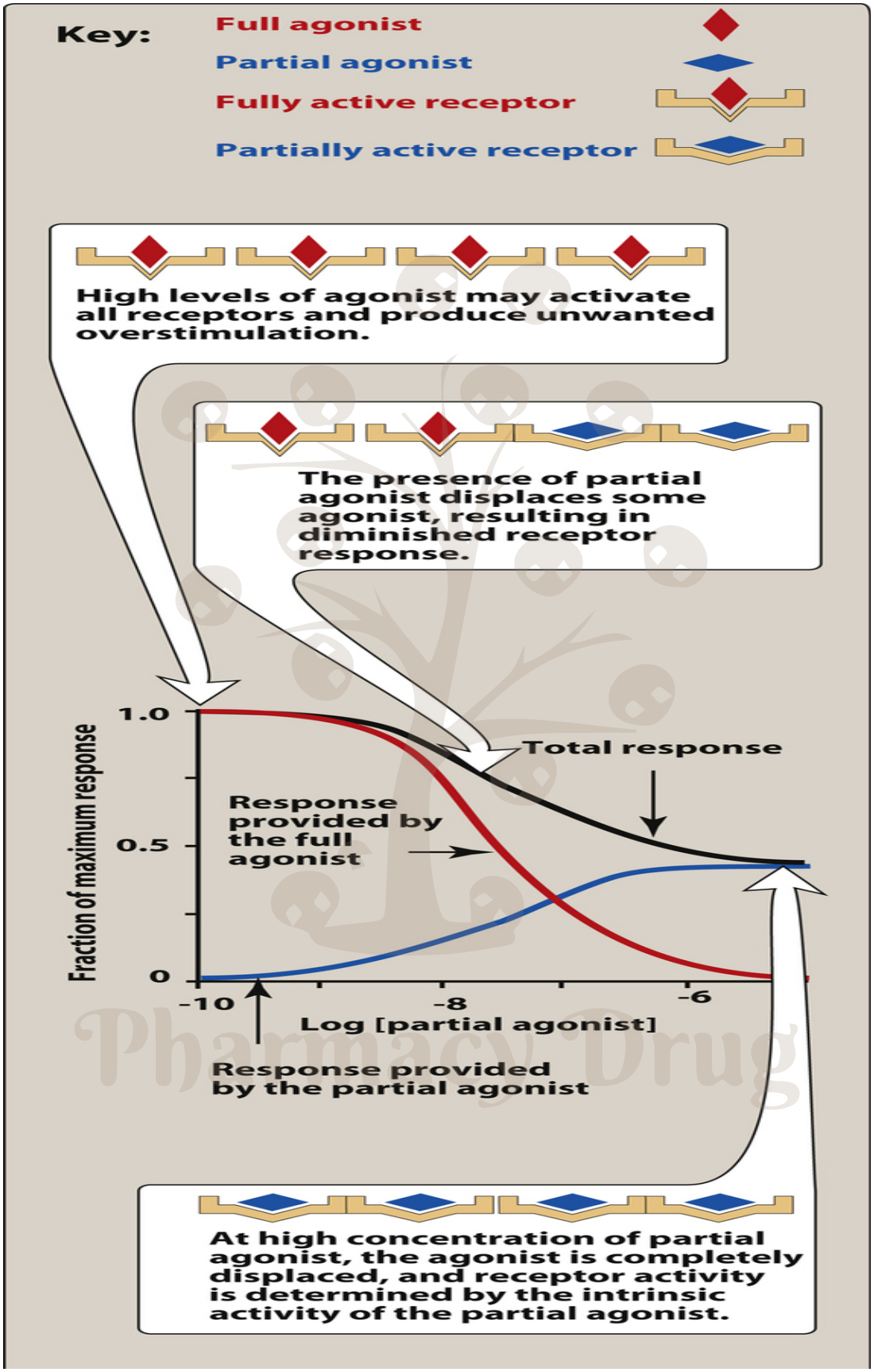

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Figure 2.12 Effects of partial agonists.

C. Inverse agonists

Typically, unbound receptors are inactive and require interaction with an agonist to assume an active conformation. However, some receptors show a spontaneous conversion from R to R* in the absence of an agonist. Inverse agonists, unlike full agonists, stabilize the inactive R form and cause R* to convert to R. This decreases the number of activated receptors to below that observed in the absence of drug (Figure 2.11). Thus, inverse agonists have an intrinsic activity less than zero, reverse the activation state of receptors, and exert the opposite pharmacological effect of agonists.

D. Antagonists

Antagonists bind to a receptor with high affinity but possess zero intrinsic activity. An antagonist has no effect on biological function in the absence of an agonist but can decrease the effect of an agonist when present. Antagonism may occur either by blocking the drug's ability to bind to the receptor or by blocking its ability to activate the receptor.

1. **Competitive antagonists:** If the antagonist binds to the same site on the receptor as the agonist in a reversible manner, it is "competitive." A competitive antagonist interferes with an agonist binding to its receptor and maintains the receptor in its inactive state. For example, the antihypertensive drug *terazosin* competes with the endogenous ligand norepinephrine at α_1-adrenoceptors, thus decreasing vascular smooth muscle tone and reducing blood pressure. However, increasing the concentration of agonist relative to antagonist can overcome this inhibition. Thus, competitive antagonists characteristically shift the agonist dose–response curve to the right (increased EC_{50}) without affecting E_{max} (Figure 2.13).

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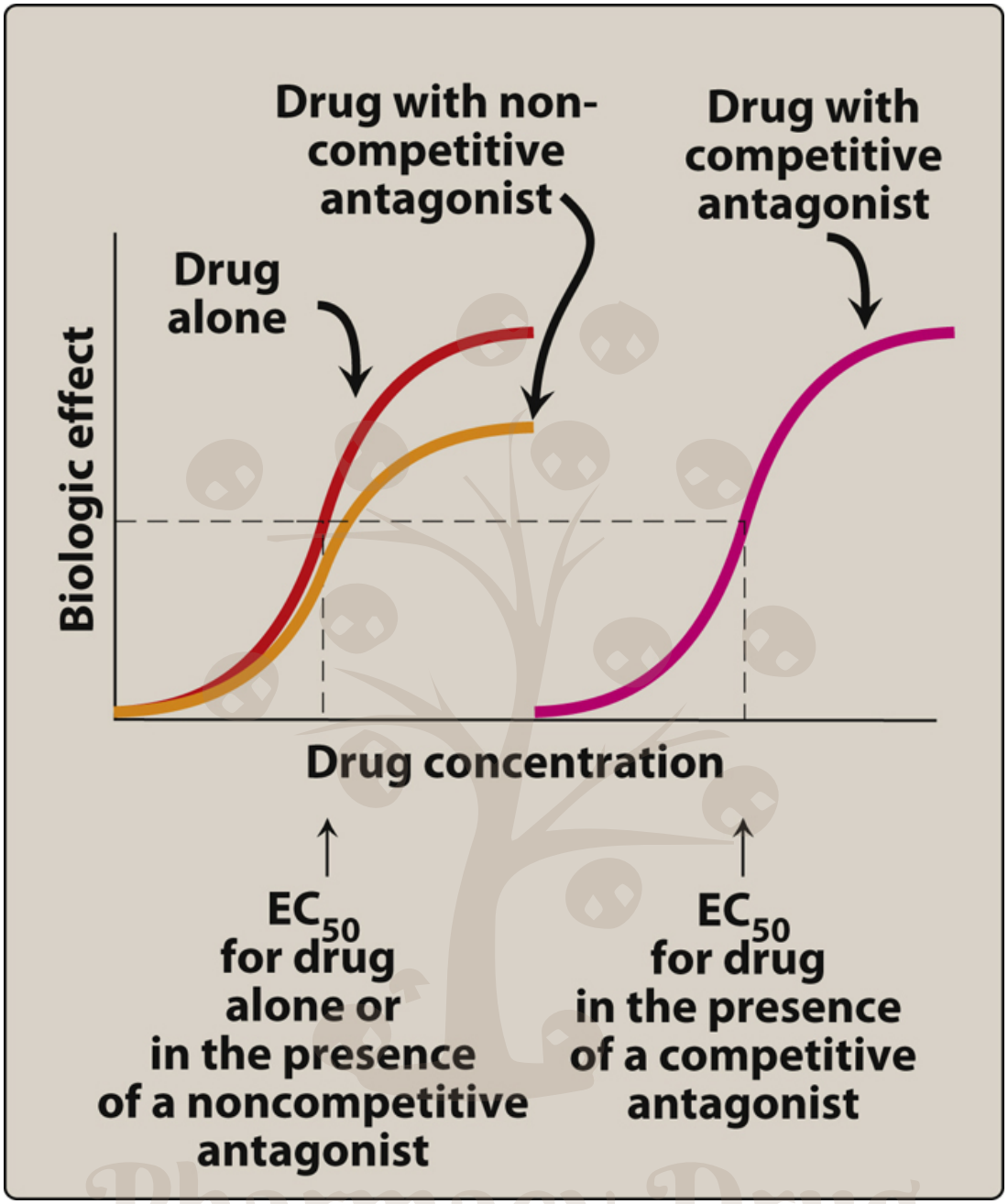

Figure 2.13 Effects of drug antagonists.EC_{50} = drug dose that shows 50% of maximal response.

2.Irreversible antagonists: Irreversible antagonists bind covalently to the active site of the receptor, thereby permanently reducing the number of receptors available to the agonist. An irreversible antagonist causes a downward shift of

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E_{max}, with no shift of EC_{50} values (Figure 2.13). In contrast to competitive antagonists, addition of more agonist does not overcome the effect of irreversible antagonists. Thus, irreversible antagonists and allosteric antagonists (see below) are both considered noncompetitive antagonists. A fundamental difference between competitive and noncompetitive antagonists is that competitive antagonists reduce agonist potency (increase EC_{50}) and noncompetitive antagonists reduce agonist efficacy (decrease E_{max}).

3. **Allosteric antagonists:** An allosteric antagonist binds to a site (allosteric site) other than the agonist-binding site and prevents receptor activation by the agonist. This type of antagonist also causes a downward shift of the E_{max} of an agonist, with no change in the EC_{50} value. An example of an allosteric agonist is picrotoxin, which binds to the inside of the GABA-controlled chloride channel. When picrotoxin binds inside the channel, no chloride can pass through the channel, even when GABA fully occupies the receptor.

4. **Functional antagonism:** An antagonist may act at a completely separate receptor, initiating effects that are functionally opposite those of the agonist. A classic example is the functional antagonism by epinephrine to histamine-induced bronchoconstriction. Histamine binds to H_1 histamine receptors on bronchial smooth muscle, causing bronchoconstriction of the bronchial tree. Epinephrine is an agonist at β_2-adrenoceptors on bronchial smooth muscle, which causes the muscles to relax. This functional antagonism is also known as "physiologic antagonism."

V. QUANTAL DOSE–RESPONSE RELATIONSHIPS

Another important dose–response relationship is that between the dose of the drug and the proportion of a population that responds to

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it. These responses are known as quantal responses, because, for any individual, either the effect occurs or it does not. Graded responses can be transformed to quantal responses by designating a predetermined level of the graded response as the point at which a response occurs or not. For example, a quantal dose–response relationship can be determined in a population for the antihypertensive drug *atenolol.* A positive response is defined as a fall of at least 5 mm Hg in diastolic blood pressure. Quantal dose–response curves are useful for determining doses to which most of the population responds. They have similar shapes as log dose–response curves, and the dose that produces a therapeutic or effective response in half of the population is designated as ED_{50}.

A. Therapeutic index

The therapeutic index (TI) of a drug is the ratio of the dose that produces toxicity in half the population (TD_{50}) to the dose that produces a clinically desired or effective response (ED_{50}) in half the population:

$$TI = TD_{50}/ED_{50}$$

The TI is a measure of safety of a drug, because a larger value indicates a wide margin between doses that are effective and doses that are toxic.

B. Clinical usefulness of the therapeutic index

The TI of a drug is determined using drug trials and accumulated clinical experience. These usually reveal a range of effective doses and a different (sometimes overlapping) range of toxic doses. Although high TI values are required for most drugs, some drugs with low therapeutic indices are routinely used to treat serious diseases. In these cases, the risk of experiencing adverse effects is not as great as the risk of leaving the disease untreated. Figure 2.14 shows the responses to *warfarin*, an oral anticoagulant with a low TI, and *penicillin*, an antimicrobial drug with a large TI.

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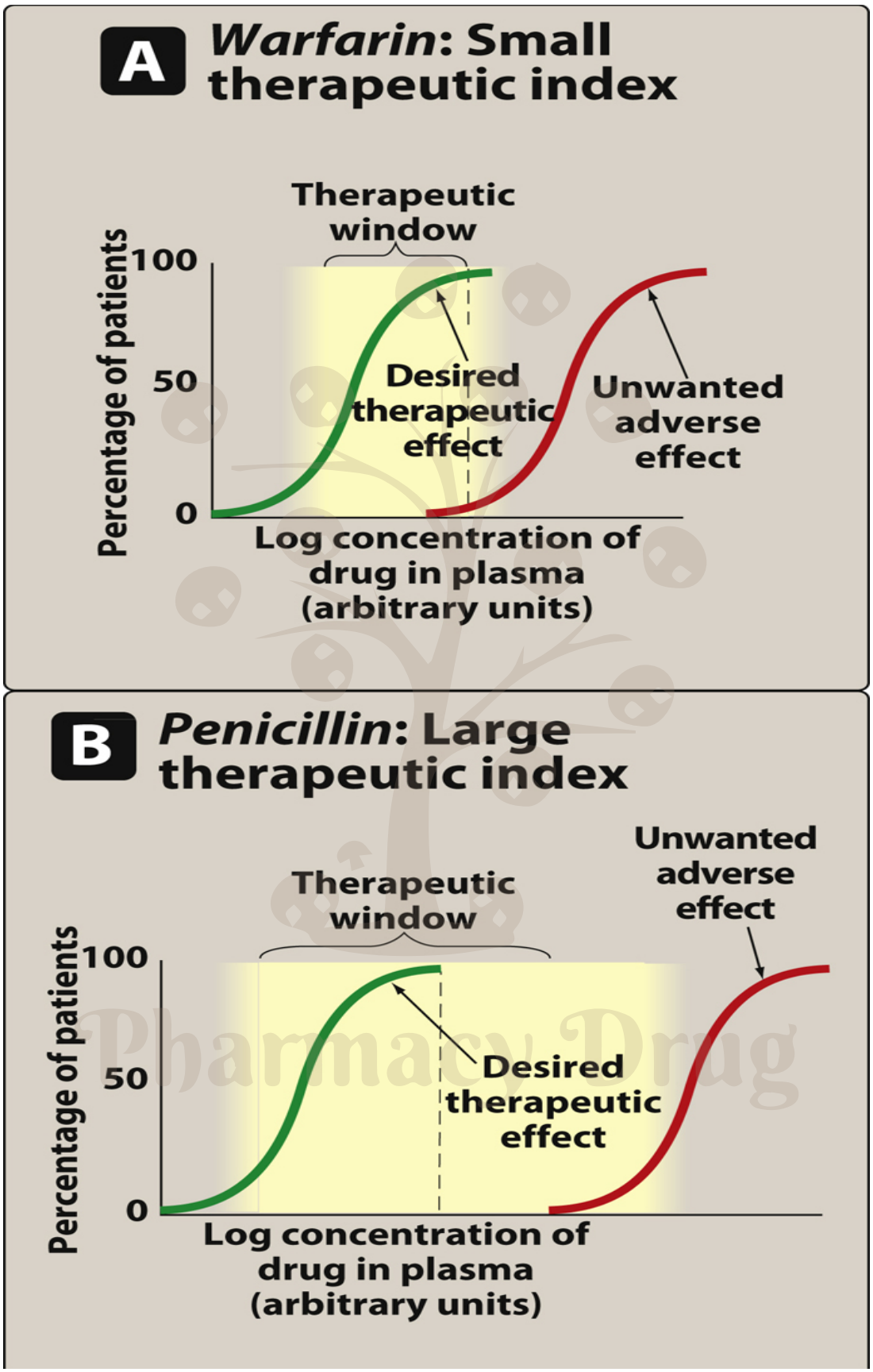

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Figure 2.14 Cumulative percentage of patients responding to plasma levels of *warfarin* (**A**) and *penicillin* (**B**).

1.*Warfarin* (Example of a drug with a small therapeutic index) As the dose of *warfarin* is increased, a greater fraction of the patients respond (for this drug, the desired response is a two- to threefold increase in the international normalized ratio [INR]) until, eventually, all patients respond (Figure 2.14A). However, at higher doses of *warfarin*, anticoagulation resulting in hemorrhage occurs in a small percentage of patients. Agents with a low TI (that is, drugs for which dose is critically important) are those drugs for which bioavailability critically alters the therapeutic effects (see Chapter 1).

2.*Penicillin* (Example of a drug with a large therapeutic index): For drugs such as *penicillin* (Figure 2.14B), it is safe and common to give doses in excess of that which is minimally required to achieve a desired response without the risk of adverse effects. In this case, bioavailability does not critically alter the therapeutic or clinical effects.

Chapter Summary

- Drugs act as signals by binding to receptor proteins that activate a cascade of intracellular effects. These intracellular events result in a change in cellular function and physiological response to the drug.
- Depending on the class of receptor protein, a different sequence of molecular events occurs to cause a cellular effect of receptor activation. These receptor-mediated events can include changes in ion transfer across the cell membrane, the generation of second messenger molecules, and alterations in gene transcription.
- Drug binding to receptors can either activate the receptor (agonist), block the receptor from activation (antagonist), or cause “reverse activation” of the receptor (inverse agonist). The direction of the drug’s effect is determined by its intrinsic activity.
- Repeated receptor activation by a drug can lead to desensitization or downregulation of receptor response.

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- Drug interaction with receptors results in a graded dose–response curve, meaning that, as drug concentration increases, response increases until all the receptors are occupied. Efficacy is the magnitude of response a drug causes when it interacts with a receptor. Potency is the drug concentration that causes half of the maximal response to a drug.
- Drugs with no intrinsic activity (antagonists) can act either in a competitive or noncompetitive fashion. Competitive antagonism can be overcome by increasing the concentration of agonist. Noncompetitive antagonists decrease agonist efficacy regardless of how much agonist is present.
- The therapeutic index is a ratio of the concentration of drug that causes unwanted adverse effects in 50% of patients to the concentration of drug that causes desired therapeutic effects in 50% of patients. A higher therapeutic index is generally a measure of safety for a drug.

STUDY QUESTIONS

Choose the ONE best answer.

2.1 Which of the following best describes how a drug that acts as an agonist at the A subtype of GABA receptors affects signal transduction in a neuron?

A. Activation of this receptor subtype alters transcription of DNA in the nucleus of the neuron.
B. Activation of this receptor subtype opens ion channels that allow sodium to enter cells and increases the chance of generating an action potential.
C. Activation of this receptor subtype opens ion channels that allow chloride to enter cells and decreases the chance of generating an action potential.
D. Activation of this receptor subtype results in G protein activation and increased intracellular second messenger levels.

Correct answer = C. The GABA-A receptor is a ligand-gated ion channel selective for chloride. Agonists for the GABA-A receptor increase opening of channels, resulting in chloride entry into the neuron, hyperpolarization, and decreased action potential events.

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2.2 If 1 mg of lorazepam produces the same anxiolytic response as 10 mg of diazepam, which of the following is correct?

A. Lorazepam is more potent than is diazepam.
B. Lorazepam is more efficacious than is diazepam.
C. Lorazepam is a full agonist, and diazepam is a partial agonist.
D. Lorazepam is a better drug to take for anxiety than is diazepam.

Correct answer = A. A drug that causes the same effect at a lower dose is more potent. B and C are incorrect because without information about the maximal effect of these drugs, no conclusions can be made about efficacy or intrinsic activity. D is incorrect because the maximal response obtained is often more important than the amount of drug needed to achieve it.

2.3 If 10 mg of oxycodone produces a greater analgesic response than does aspirin at any dose, which of the following is correct?

A. Oxycodone is more efficacious than is aspirin.
B. Oxycodone is less potent than is aspirin.
C. Aspirin is a full agonist, and oxycodone is a partial agonist.
D. Oxycodone and aspirin act on the same drug target.

Correct answer = A. Drugs with greater response at maximally effective concentrations are more efficacious than drugs with a lower maximal response. Choice B is incorrect since no information is given about the half maximal concentrations of either drug. Choices C and D are incorrect since it is not known if both drugs bind to the same receptor population.

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2.4 Diazepam, flumazenil, and the experimental drug RO15-4513 all bind reversibly to the benzodiazepine receptor. Diazepam is the classic agonist for this receptor, and when it occupies the receptor, it decreases the chance of neuronal hyperexcitability, thereby decreasing seizure sensitivity. When flumazenil binds to the benzodiazepine receptor, it does not alter neuronal hyperexcitability or seizure sensitivity. Which of the following best describes the activity of flumazenil?

A. Partial agonist
B. Competitive antagonist
C. Noncompetitive antagonist
D. Inverse agonist

Correct answer = B. Flumazenil binds reversibly to the same receptor site as diazepam but has no action. Therefore, it is a competitive antagonist. A is incorrect since flumazenil would have to have some antiseizure activity (but not as much as diazepam) to be classified as a partial agonist. C is incorrect because flumazenil would have to bind irreversibly to be a noncompetitive antagonist. D is incorrect because flumazenil does not cause the opposite response as diazepam.

2.5 In the presence of picrotoxin, diazepam is less efficacious at causing sedation, regardless of the dose of diazepam. Picrotoxin has no sedative effect, even at the highest dose. Which of the following is correct regarding these agents?

A. Picrotoxin is a competitive antagonist.
B. Picrotoxin is a noncompetitive antagonist.
C. Diazepam is less efficacious than is picrotoxin.
D. Diazepam is less potent than is picrotoxin.

Correct answer = B. Since picrotoxin decreases the maximal effect of diazepam regardless of the diazepam dose, it is a noncompetitive antagonist. Picrotoxin has no efficacy alone, so C

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is incorrect. No information is provided about potency of either drug.

2.6 When albuterol binds to the beta-adrenergic receptor, it dissociates after a few milliseconds. However, its cellular actions last for hundreds of milliseconds due to the generation of second messenger molecules whose actions on effector systems take longer to occur. Which of the following best describes this phenomenon?

A. Signal amplification
B. Desensitization
C. Downregulation of receptors
D. Tachyphylaxis

Correct answer = A. Signal amplification is when the initial receptor binding event results in a cascade of subsequent molecular events that last longer in duration (and cause cellular effects of longer duration). B is incorrect because desensitization is when overactivity of receptors results in a decrease in signal transduction. C is incorrect because downregulation occurs when overactivation of receptors causes a decrease in receptor number. D is incorrect because tachyphylaxis is another name for desensitization.

2.7 If there were spare β_1-adrenergic receptors on cardiac muscle cells, which of the following statements would be correct?

A. The number of spare β_1-adrenergic receptors determines the size of the maximum effect of the agonist epinephrine.
B. Spare β_1 adrenergic receptors make the cardiac tissue less sensitive to epinephrine.
C. A maximal effect of epinephrine is seen when only a portion of β_1 adrenergic receptors are occupied.
D.

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Spare receptors are active even in the absence of epinephrine.

Correct answer = C. Only a fraction of the total receptors need to be bound to elicit a maximum cellular response when spare receptors are present. The other choices do not accurately describe the effects of having spare receptors.

2.8 Which of the following upregulates postsynaptic α_1-adrenergic receptors?

A. Daily use of amphetamine that causes release of norepinephrine
B. A disease that causes an increase in the activity of norepinephrine neurons
C. Daily use of phenylephrine, an α_1 receptor agonist
D. Daily use of prazosin, an α_1 receptor antagonist

Correct answer = D. Upregulation of receptors occurs when receptor activation is lower than normal, such as when the receptor is continuously exposed to an antagonist for that receptor. Downregulation of receptors occurs when receptor activation is greater than normal because of continuous exposure to an agonist, as described in A, B, and C.

2.9 Methylphenidate helps patients with attention deficit hyperactivity disorder (ADHD) maintain attention and perform better at school or work, with an ED_{50} of 10 mg. However, methylphenidate can also cause significant nausea at higher doses (TD_{50} = 30 mg). Which of the following is correct regarding methylphenidate?

A. The therapeutic index of methylphenidate is 3.
B. The therapeutic index of methylphenidate is 0.3.
C.

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Methylphenidate is more potent at causing nausea than treating ADHD.
D. Methylphenidate is more efficacious at causing nausea than treating ADHD.

Correct answer = A. Therapeutic index is calculated by dividing TD_{50} by ED_{50} (30/10), making B incorrect. C is incorrect because methylphenidate is more potent at treating ADHD (it takes a lower dose) than causing nausea. D. No information about efficacy is provided.

2.10 Which of the following is correct concerning the safety of using warfarin (with a small therapeutic index) versus penicillin (with a large therapeutic index)?

A. Warfarin is a safer drug because it has a low therapeutic index.
B. Warfarin treatment has a high chance of resulting in dangerous adverse effects if bioavailability is altered.
C. The high therapeutic index makes penicillin a safe drug for all patients.
D. Penicillin treatment has a high chance of causing dangerous adverse effects if bioavailability is altered.

Correct answer = B. Agents with a low TI (that is, drugs for which dose is critically important) are those drugs for which bioavailability critically alters the therapeutic and adverse effects. A is incorrect, because a drug with a low TI is not generally considered to be safe. C is incorrect because a high TI does not ensure safety across the entire patient population. D is incorrect because the high TI makes it unlikely that bioavailability alters the incidence of therapeutic or adverse effects.

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UNIT II:
Drugs Affecting the Autonomic Nervous System

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3

The Autonomic Nervous System

David Skyba, Rajan Radhakrishnan

I. OVERVIEW

The autonomic nervous system (ANS), along with the endocrine system, coordinates the regulation and integration of bodily functions. The endocrine system sends signals to target tissues by varying the levels of blood-borne hormones. By contrast, the nervous system exerts effects by the rapid transmission of electrical impulses over nerve fibers that terminate at effector cells, which specifically respond to the release of neuromediator substances. Drugs that produce their primary therapeutic effect by mimicking or altering the functions of the ANS are called autonomic drugs and are discussed in the following four chapters. The autonomic agents act either by stimulating portions of the ANS or by blocking the actions of the ANS. This chapter outlines the fundamental physiology and anatomy of the ANS and describes the role of neurotransmitters in the communication between extracellular events and chemical changes within the cell.

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II. INTRODUCTION TO THE NERVOUS SYSTEM

The nervous system is divided into two anatomical divisions: the central nervous system (CNS), which is composed of the brain and

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spinal cord, and the peripheral nervous system (PNS), which includes nerves that connect the CNS with peripheral structures (Figure 3.1). The PNS is subdivided into the efferent and afferent divisions. The efferent neurons carry signals away from the brain and spinal cord to the peripheral tissues, and the afferent neurons bring information from the periphery to the CNS. Afferent neurons provide sensory input to modulate the function of the efferent division through reflex arcs or neural pathways that mediate a reflex action.

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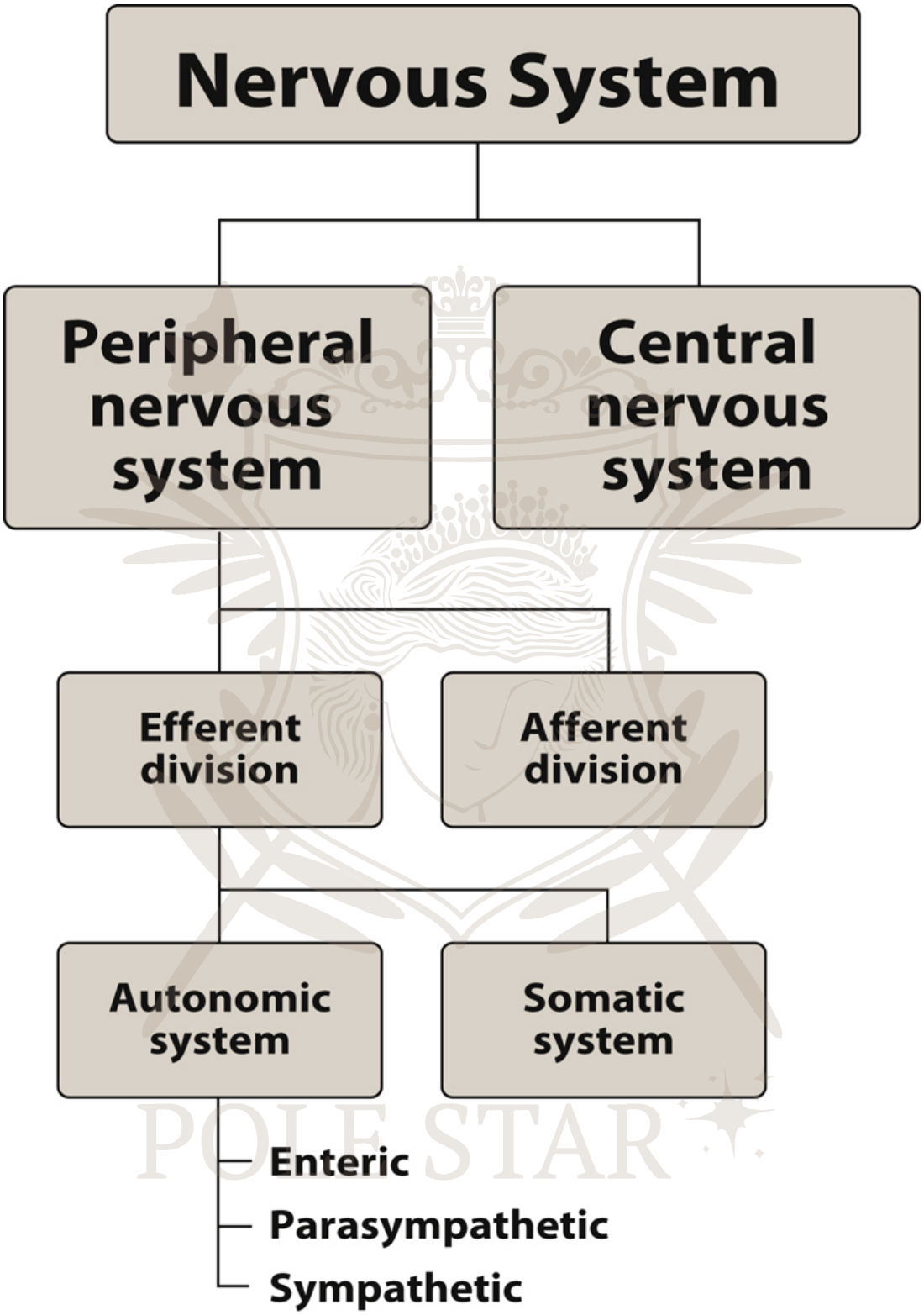

Figure 3.1 Organization of the nervous system.

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A. Functional divisions within the nervous system

The efferent portion of the PNS is further divided into two major functional subdivisions: the somatic nervous system and the ANS (Figure 3.1). The somatic efferent neurons are involved in the voluntary control of functions such as contraction of the skeletal muscles essential for locomotion. The ANS, conversely, regulates the everyday requirements of vital bodily functions without conscious participation of the mind. Because of the involuntary nature of the ANS as well as its functions, it is also known as the visceral, vegetative, or involuntary nervous system. It is composed of efferent neurons that innervate visceral smooth muscle, cardiac muscle, vasculature, and the exocrine glands, thereby controlling digestion, cardiac output, blood flow, and glandular secretions.

B. Anatomy of the ANS

1. **General organization:** The ANS carries efferent nerve impulses from the CNS to effector organs through a two-neuron pathway consisting of a **preganglionic neuron** and a **postganglionic neuron** (Figure 3.2). The cell body of the first nerve cell, the preganglionic neuron, is located within the CNS, while the cell body of the postganglionic neuron is found within a **ganglion** (a collection of neuron cell bodies in the PNS). The ganglion functions as a relay station for communication between the preganglionic neuron and the second nerve cell, the postganglionic neuron. The lightly myelinated axons of the preganglionic neurons emerge from the brainstem and spinal cord via cranial and spinal nerves, respectively, and travel to autonomic ganglia. Here they synapse with the postganglionic neurons. The unmyelinated axons of the postganglionic neurons then complete the second part of the pathway to terminate on effector organs in the periphery, such as visceral smooth muscle, cardiac muscle, and exocrine glands.

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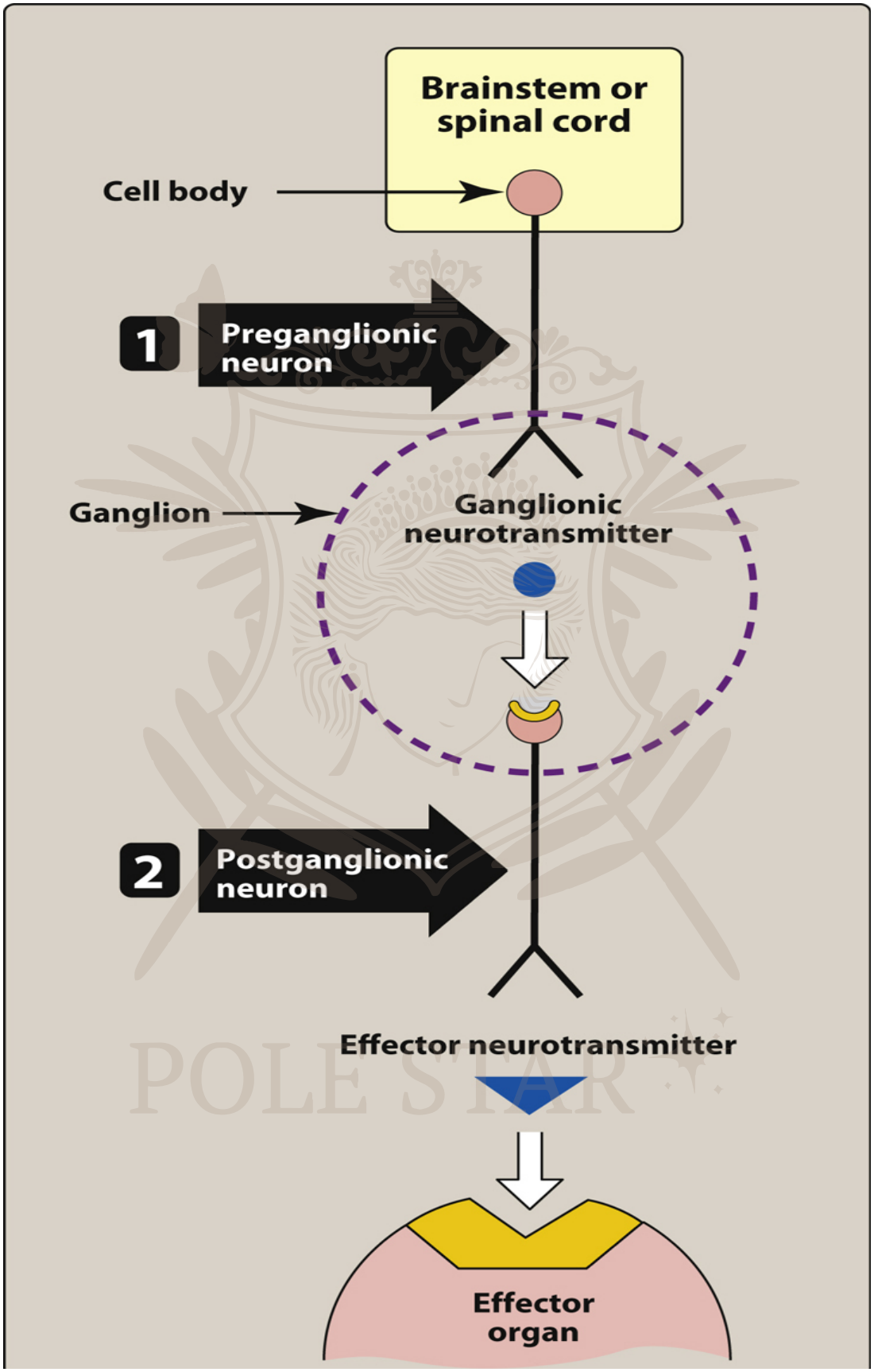
Brainstem or spinal cord
Cell body
1
Preganglionic neuron
Ganglion
Ganglionic neurotransmitter
2
Postganglionic neuron
Effector neurotransmitter
Effector organ

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Figure 3.2 Efferent neurons of the autonomic nervous system.

The ANS has three functional divisions: the sympathetic nervous system, the parasympathetic nervous system, and the enteric nervous system (Figure 3.1).

2.Sympathetic nervous system: The sympathetic division of the ANS is organized anatomically such that its relatively short preganglionic fibers emerge from the thoracic and upper lumbar spinal cord and terminate in either paravertebral or prevertebral ganglia located in close proximity to the vertebral column (Figure 3.3). For this reason, the sympathetic nervous system (SNS) is also referred to as the thoracolumbar division of the ANS. Preganglionic sympathetic neurons are found within the lateral horn of the spinal gray matter (intermediolateral cell column) at segmental levels T1-L2. Their axons travel through ventral roots to the spinal nerves at these levels and then to the ganglia of the sympathetic trunk (paravertebral ganglia) via white communicating branches. Generally, preganglionic sympathetic fibers exhibit a high degree of branching, enabling a single preganglionic neuron to contact multiple postganglionic neurons within one or more ganglia. This arrangement enables the segmental spinal outflow of the SNS to activate a large number of widespread effector organs at the same time. [Note: The adrenal medulla is directly innervated by preganglionic sympathetic neurons. In response to stimulation by the ganglionic neurotransmitter, acetylcholine, the chromaffin cells of the adrenal medulla secrete epinephrine (adrenaline), and lesser amounts of norepinephrine, directly into the bloodstream.] Postganglionic sympathetic neurons have much longer axons that are distributed to their effector targets (Figure 3.3) through spinal nerves, splanchnic (visceral) nerves, or nerve plexuses surrounding blood vessels. [Note: Postganglionic fibers enter

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the spinal nerves through gray communicating branches and reach their targets through branches of the peripheral nerves.]

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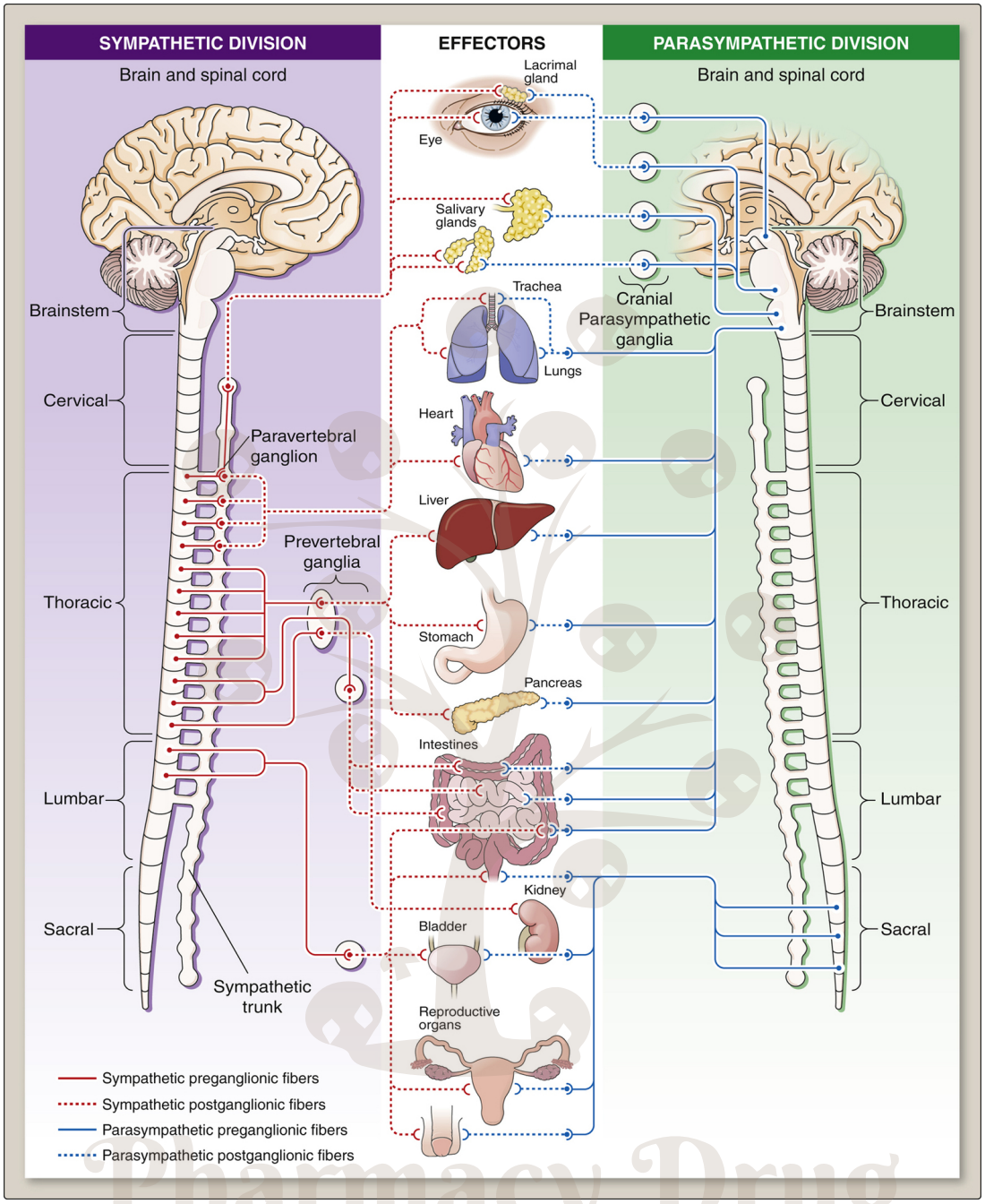

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Figure 3.3 Autonomic nervous system.Modified from B. J.Cohen and K. L.Hull . *Memmler's Structure and Function of the Human Body*, 12th ed. Philadelphia, PA, Wolters Kluwer (2020), Figure 8.14, with permission.

3.Parasympathetic nervous system: The parasympathetic nervous system (PSNS) is characterized by

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long preganglionic fibers that originate in the brainstem and sacral region (segments S2 to S4) of the spinal cord. Thus, it may also be referred to as the craniosacral division of the ANS. Cranial nerves III (oculomotor nerve), VII (facial nerve), and IX (glossopharyngeal nerve) carry preganglionic fibers to discrete cranial parasympathetic ganglia, which contain postganglionic neurons that innervate effectors of the head. The majority of the preganglionic parasympathetic fibers leave the CNS within cranial nerve X (vagus nerve) for distribution to ganglia associated with the organs of the thoracic cavity and most of the abdominal viscera, while the sacral preganglionic fibers exit through pelvic splanchnic nerves and ultimately are distributed to ganglia associated with the bladder, reproductive organs, and gastrointestinal (GI) tract distal to the left colic flexure. In contrast to the SNS, the postganglionic parasympathetic fibers are short with a relatively narrow distribution. In addition, the ratio of preganglionic to postganglionic parasympathetic neurons is low (often one-to-few), and this anatomical organization allows for more selective control of effectors.

4. **Enteric nervous system:** The enteric nervous system is the third division of the ANS. It is a collection of neurons that innervate the GI tract, pancreas, and gallbladder, and it constitutes the “brain of the gut.” This system functions independently of the CNS and controls motility, exocrine and endocrine secretions, and microcirculation of the GI tract. It is modulated by both the sympathetic and parasympathetic nervous systems.

C. Functions of the sympathetic nervous system

Although continually active to some degree (for example, in maintaining tone of vascular beds), the sympathetic division is responsible for adjusting bodily functions in response to stressful situations, such as trauma, fear, hypoglycemia, cold, and exercise (Figure 3.4).

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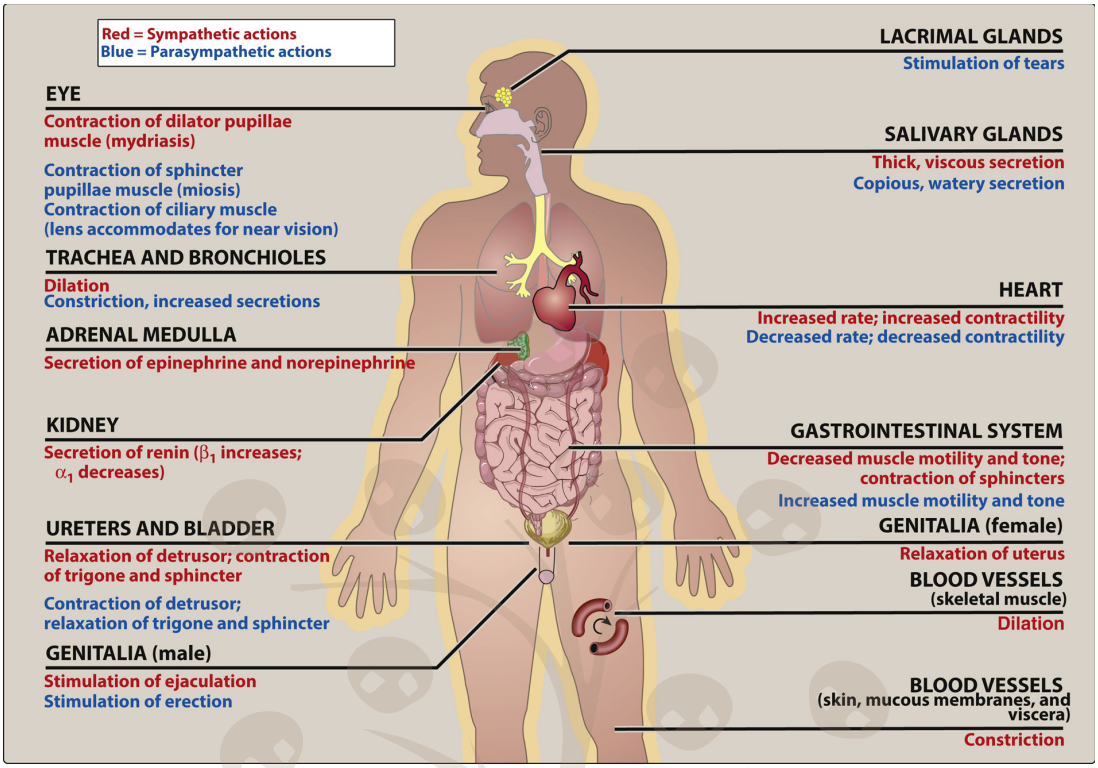

Figure 3.4 Actions of sympathetic and parasympathetic nervous systems on effector organs.

1.Effects of stimulation of the sympathetic division: The major effect of sympathetic stimulation is an increase in cardiac output and blood pressure, mobilization of energy stores, and increase in blood flow to skeletal muscles and the heart while diverting flow from the skin and splanchnic system (GI tract, liver, pancreas, and spleen). Sympathetic stimulation results in dilation of the pupils (mydriasis) and bronchioles (Figure 3.4). It also reduces GI motility and affects function of the bladder and sexual organs.

2.Fight or flight response: The changes experienced by the body during emergencies are referred to as the "fight or flight" response (Figure 3.5). These reactions are triggered both by direct sympathetic activation of effector organs and by stimulation of the adrenal medulla to release epinephrine and a lesser amount of norepinephrine. Hormones released by the

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adrenal medulla directly enter the bloodstream and promote responses in effector organs that contain adrenergic receptors (see Chapter 6). The SNS tends to function as a unit and often discharges as a complete system as can be seen during strenuous exercise or in reactions to fearful situations (Figure 3.5). This system, with its diffuse distribution of postganglionic fibers, is involved in a wide array of physiologic activities and is essential in preparing the body to handle uncertain situations and unexpected stimuli.

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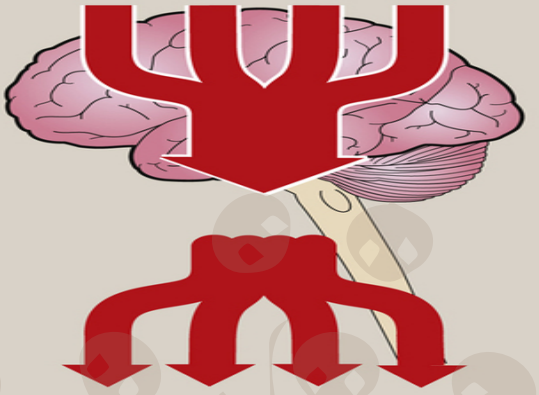
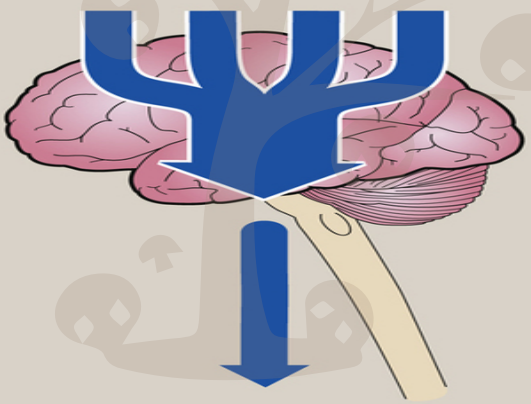
"Fight-or-flight" stimulus



Sympathetic output
(diffuse because postganglionic neurons may innervate more than one organ)

"Rest-and-digest" stimulus



Parasympathetic output
(discrete because postganglionic neurons are not branched, but are directed to a specific organ)

Sympathetic and para-sympathetic actions often oppose each other

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Figure 3.5 Sympathetic and parasympathetic actions are elicited by different stimuli.

D. Functions of the parasympathetic nervous system

The parasympathetic division is involved in maintaining homeostasis within the body. It is required for life, since it maintains essential bodily functions, such as digestion and excretion. The parasympathetic division usually acts to oppose or balance the actions of the sympathetic division and generally predominates in "rest-and-digest" situations. Unlike the sympathetic system, the parasympathetic system never discharges as a complete system. If it did, it would produce massive, undesirable, and unpleasant symptoms, such as involuntary salivation, urination, and defecation. Instead, parasympathetic fibers innervating specific organs such as the gut, heart, or eye are activated separately, and the system affects these organs individually.

E. Role of the CNS in the control of autonomic functions

Although the ANS is a visceromotor system, it does require sensory input from peripheral structures to provide information on the current state of the body. This feedback is provided by streams of afferent impulses, originating in the viscera and other autonomically innervated structures that travel to integrating centers in the CNS, such as the hypothalamus, medulla oblongata, and spinal cord. These centers respond by adjusting the output of the ANS, which regulates vital body functions and helps to maintain homeostasis.

1. **Reflex arcs:** Most of the afferent impulses are involuntarily translated into reflex responses. For example, a fall in blood pressure causes pressure-sensitive neurons (baroreceptors in the aortic arch and carotid sinuses) to send fewer impulses to cardiovascular centers in the brain. This

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prompts a reflex response of increased sympathetic output to the heart and vasculature and decreased parasympathetic output to the heart, which results in a compensatory rise in blood pressure, contractility, and heart rate (Figure 3.6). [Note: In each case, the reflex arcs of the ANS comprise a sensory (afferent) arm and a motor (efferent or effector) arm.]

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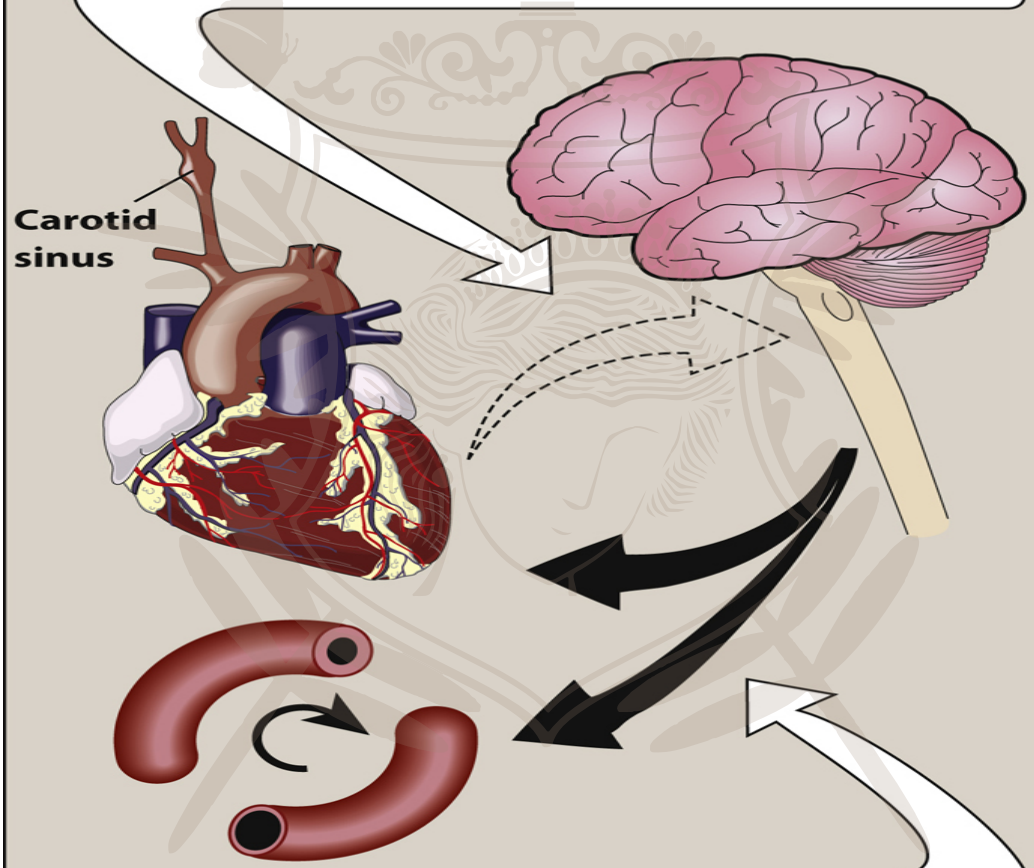
1 AFFERENT INFORMATION

Sensory input from the viscera:

- Drop in blood pressure
- Reduced stretch of baroreceptors in the aortic arch and carotid sinuses
- Reduced frequency of afferent impulses to the medulla (brainstem)



2 REFLEX RESPONSE

Inhibition of the parasympathetic division and activation of the sympathetic division of the ANS causes:

- Increase in heart rate and contractility (+SNS, -PSNS)
- Constriction of blood vessels (+SNS)
- Increase in cardiac output and peripheral resistance
- Increase in blood pressure

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Figure 3.6 Baroreceptor reflex arc response to a decrease in blood pressure.

2.Emotions and the ANS: Stimuli that evoke strong feelings, such as anger, fear, and pleasure, can modify activities of the ANS.

F. Innervation by the ANS

Most organs are innervated by both divisions of the ANS. Thus, parasympathetic innervation slows the heart rate, and sympathetic innervation increases heart rate. Despite this dual innervation, one system usually predominates in controlling the activity of a given organ. For example, the vagus nerve (cranial nerve X) is the predominant factor for controlling heart rate. The dual innervation of organs is dynamic and fine-tuned continually to maintain homeostasis. Although most tissues receive dual innervation, some effector organs, such as the adrenal medulla, kidney, pilomotor muscles, and sweat glands, receive innervation only from the sympathetic system.

G. Somatic nervous system

The somatic motor system differs from the ANS in that its myelinated motor fibers travel from the CNS to directly innervate skeletal muscle with no intervening ganglia. As noted earlier, the somatic nervous system is under voluntary control, whereas the ANS is involuntary. Responses in the somatic division are generally faster than those in the ANS.

H. Summary of differences between sympathetic, parasympathetic, and motor nerves

Major differences in the anatomical arrangement of neurons lead to variations of the functions in each division (Figure 3.7). The SNS is widely distributed, innervating practically all effector systems in the body. By contrast, the distribution of the

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parasympathetic division is more limited. The sympathetic preganglionic fibers have a much broader influence than the parasympathetic fibers and synapse with a larger number of postganglionic neurons. This type of organization permits a diffuse discharge of the SNS. The parasympathetic division is more circumscribed, with mostly one-to-few interactions, and the ganglia are also close to, or within, the organs they innervate. This limits the amount of branching that can occur with this division. [A notable exception is found in the myenteric plexus (major nerve supply to the GI tract), where one preganglionic neuron has been shown to interact with several thousand postganglionic fibers.] The anatomical arrangement of the parasympathetic system results in the distinct functions of this division. The somatic nervous system innervates skeletal muscles. The axons of somatic motor neurons are highly branched, with each of the terminal branches innervating a single muscle fiber. Thus, one somatic motor neuron may innervate a large number of muscle fibers. This arrangement leads to the formation of a motor unit. The lack of ganglia and the myelination of the motor neurons enables a fast response by the somatic nervous system.

	SYMPATHETIC	PARASYMPATHETIC
Sites of origin	Thoracic and lumbar region of the spinal cord (thoracolumbar)	Brainstem and sacral area of the spinal cord (craniosacral)
Length of fibers	Short preganglionic Long postganglionic	Long preganglionic Short postganglionic
Location of ganglia	Close to the spinal cord	Within or near effector organs
Preganglionic fiber branching	Extensive	Minimal
Distribution	Wide	Limited
Type of response	Diffuse	Discrete

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Figure 3.7 Characteristics of the sympathetic and parasympathetic nervous systems.

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III. CHEMICAL SIGNALING BETWEEN CELLS

Neurotransmission in the ANS is an example of chemical signaling between cells. In addition to neurotransmission, other types of chemical signaling include the secretion of hormones and the release of local mediators (Figure 3.8).

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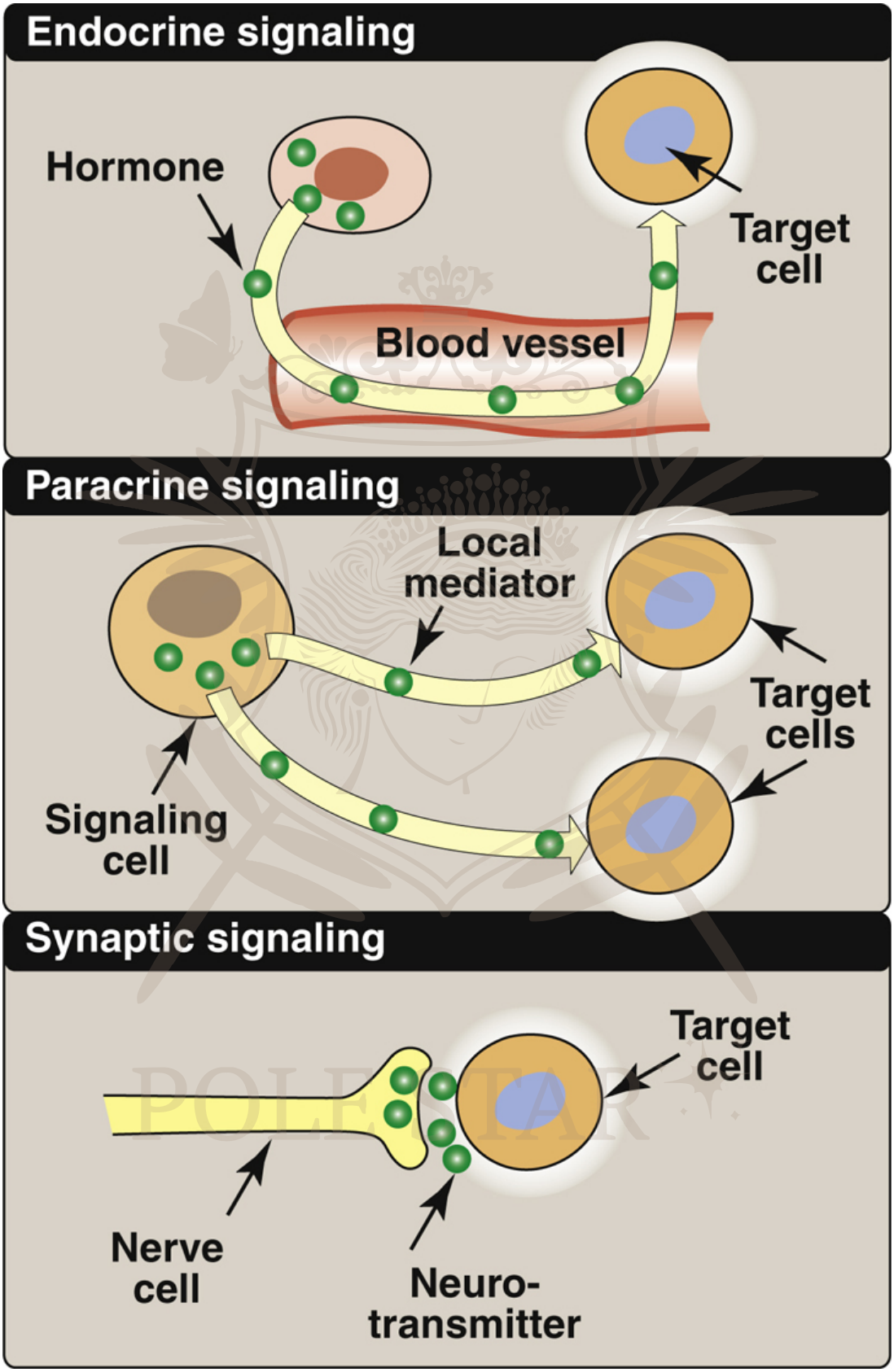
Endocrine signaling
Hormone
Target cell
Blood vessel
Paracrine signaling
Local mediator
Target cells
Signaling cell
Synaptic signaling
Target cell
Nerve cell
Neuro-transmitter

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Figure 3.8 Some commonly used mechanisms for transmission of regulatory signals between cells.

A. Hormones

Specialized endocrine cells secrete hormones into the bloodstream, where they travel throughout the body, exerting effects on broadly distributed target cells (see Chapters 23 through 26).

B. Local mediators

Most cells secrete chemicals that act locally on cells in the immediate environment. Because these chemical signals are rapidly destroyed or removed, they do not enter the blood and are not distributed throughout the body. Histamine (see Chapter 39) and prostaglandins are examples of local mediators.

C. Neurotransmitters

Communication between nerve cells, and between nerve cells and effector organs, occurs through the release of specific chemical signals (neurotransmitters) from the nerve terminals. The release is triggered by arrival of the action potential at the axon terminals, leading to depolarization of the cell membrane. The resulting increase in intracellular Ca^{2+} initiates fusion of synaptic vesicles with the presynaptic membrane and release of their contents. The neurotransmitters rapidly diffuse across the synaptic cleft (synaptic space) and bind with specific receptors on the postsynaptic (target) cell.

1. Membrane receptors: All neurotransmitters, and most hormones and local mediators, are too hydrophilic to penetrate the lipid bilayers of target cell plasma membranes. Instead, their signal is mediated by binding to specific receptors on the cell surface of target organs. [Note: A receptor is defined as a recognition site for a substance. It has a binding specificity and

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is coupled to processes that eventually evoke a response. Most receptors are proteins (see Chapter 2).]

2.Types of neurotransmitters: Although over 50 signaling molecules in the nervous system have been identified, norepinephrine (and the closely related epinephrine), acetylcholine, dopamine, serotonin, histamine, glutamate, and γ-aminobutyric acid are most commonly involved in the actions of therapeutically useful drugs. Each of these chemical signals binds to a specific family of receptors. Acetylcholine and norepinephrine are the primary chemical signals in the ANS, whereas a wide variety of neurotransmitters function in the CNS.

3.Acetylcholine: The autonomic nerve fibers can be divided into two groups based on the type of neurotransmitter released. If transmission is mediated by acetylcholine, the neuron is termed cholinergic (Figure 3.9 and Chapters 4 and 5). Acetylcholine mediates the transmission of nerve impulses across autonomic ganglia in both the sympathetic and parasympathetic nervous systems. It is the neurotransmitter at the adrenal medulla. Transmission from the autonomic postganglionic fibers to the effector organs in the parasympathetic system, and a few sympathetic system effectors, also involves the release of acetylcholine. In the somatic nervous system, transmission at the neuromuscular junction (the junction of nerve fibers and skeletal muscle) is also cholinergic (Figure 3.9).

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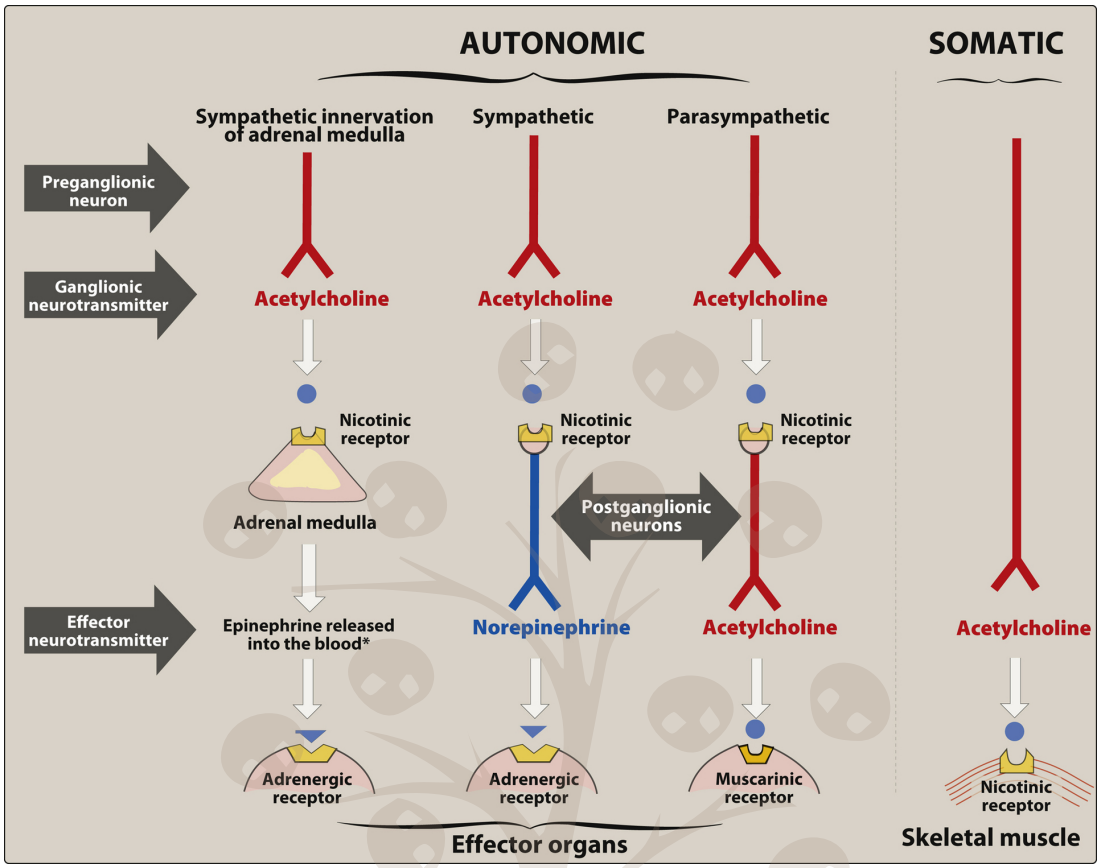

Figure 3.9 Summary of the neurotransmitters released, types of receptors, and types of neurons within the autonomic and somatic nervous systems.Cholinergic neurons are shown in *red* and adrenergic neurons in *blue.* [Note: This schematic diagram does not show that the parasympathetic ganglia are close to or on the surface of the effector organs and that the postganglionic fibers are usually shorter than the preganglionic fibers. By contrast, the ganglia of the sympathetic nervous system are close to the spinal cord. The postganglionic fibers are long, allowing extensive branching.] *Epinephrine 80% and norepinephrine 20% released from adrenal medulla.

4.Norepinephrine and epinephrine: When norepinephrine is the neurotransmitter, the fiber is termed adrenergic (Figure 3.9 and Chapters 6 and 7). In the sympathetic system, norepinephrine mediates the transmission of nerve impulses from autonomic postganglionic

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neurons to effector organs. Epinephrine secreted by the adrenal medulla (not sympathetic neurons) also acts as a chemical messenger in the effector organs. [Note: Some sympathetic fibers, such as those innervating sweat glands, are cholinergic. For simplicity, they are not shown in Figure 3.9.]

Clinical Application 3.1 Understanding the Role of the SNS and PSNS in Pharmacologic Strategies

Understanding the basic functions of the sympathetic and parasympathetic nervous system (SNS and PSNS) mediated by neurotransmitters in modulating the function of various tissues and organs in the body is crucial to understanding the mechanisms of pharmacologic agents that act on these systems. Although this chapter does not describe the actions of sympathetic or parasympathetic systems at the receptor level, it provides an overview of the physiologic effects caused by the neurotransmitters involved in these systems. For example, activation of the SNS leads to an increase in heart rate, increased force of contraction of the heart, and vasoconstriction that results in an increase in blood pressure. These actions are mediated mainly by two neurotransmitters, epinephrine and norepinephrine, acting on adrenergic receptors located in the heart and blood vessels. Inhibiting the actions of these neurotransmitters in the heart and/or blood vessels can theoretically reduce blood pressure. Similarly, overactivity of the PSNS via acetylcholine acting on muscarinic receptors in the GI tract will increase motility and secretions. Inhibiting the actions of acetylcholine on muscarinic receptors can therefore theoretically reverse these changes. Thus, understanding the general physiologic effects of the SNS and PSNS helps to predict and formulate pharmacologic strategies that can be used to treat conditions caused by the overactivity or inactivity of these systems.

IV. SIGNAL TRANSDUCTION IN THE EFFECTOR CELL

The binding of chemical signals to receptors activates enzymatic processes within the cell membrane that ultimately results in a cellular response, such as the phosphorylation of intracellular proteins or changes in the conductivity of ion channels (see Chapter

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2). A neurotransmitter can be thought of as a signal and a receptor as a signal detector and transducer. The receptors in the ANS effector cells are classified as adrenergic or cholinergic based on the neurotransmitters or hormones that bind to them. Epinephrine and norepinephrine bind to adrenergic receptors, and acetylcholine binds to cholinergic receptors. Cholinergic receptors are further classified as nicotinic or muscarinic. Some receptors, such as the postsynaptic cholinergic nicotinic receptors in skeletal muscle cells, are directly linked to membrane ion channels and are known as ionotropic receptors. Binding of neurotransmitter to ionotropic receptors directly affects ion permeability (Figure 3.10A). All adrenergic receptors and cholinergic muscarinic receptors are G protein–coupled receptors (metabotropic receptors). Metabotropic receptors mediate the effects of ligands by activating a second messenger system inside the cell. The two most widely recognized second messengers are the adenylyl cyclase system and the calcium/phosphatidylinositol system (Figure 3.10B and C).

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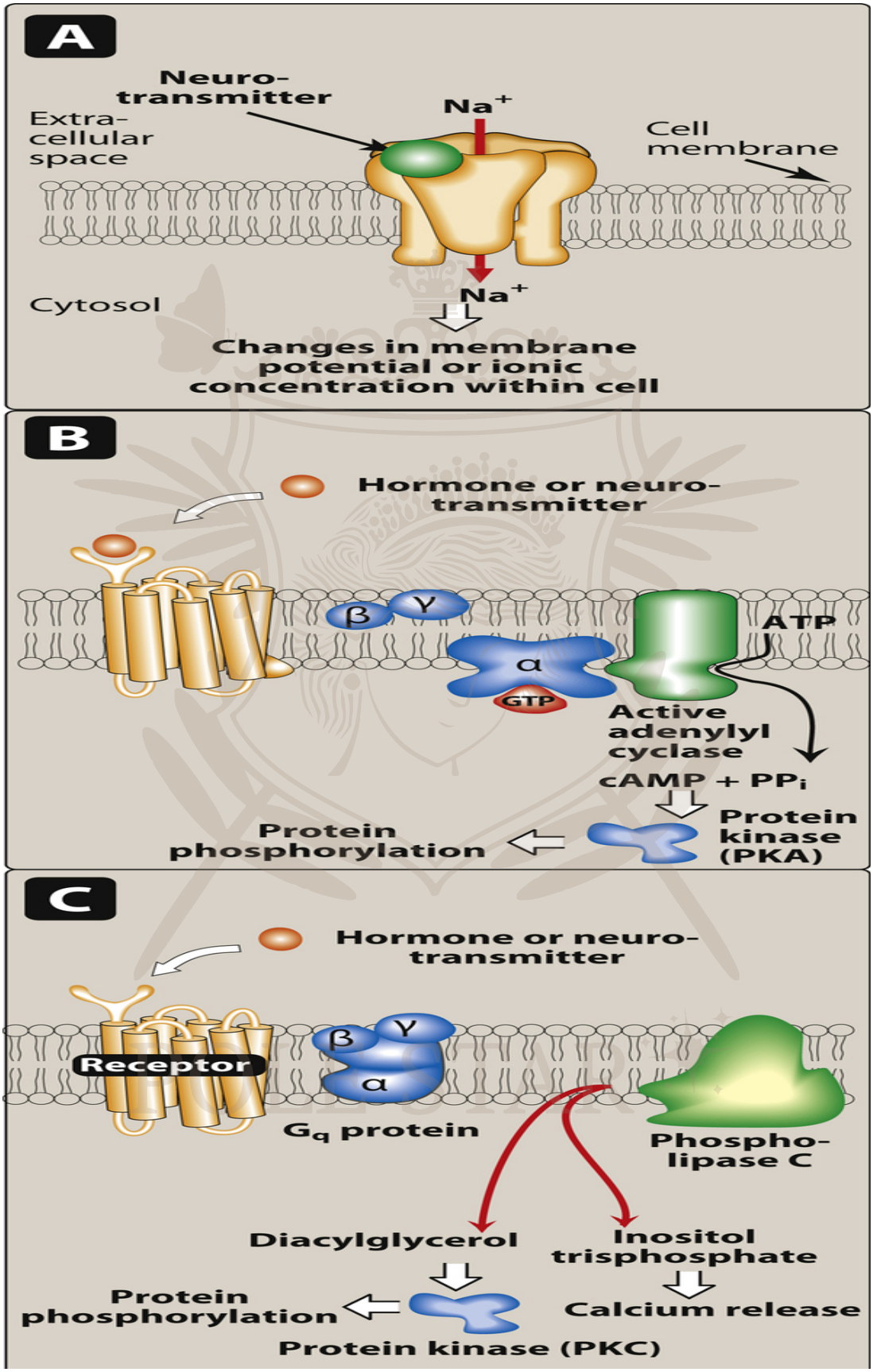
A
Neuro-
transmitter
Extra-
cellular
space
Na+
Cell
membrane
Cytosol
Na+
Changes in membrane
potential or ionic
concentration within cell
B
Hormone or neuro-
transmitter
β
γ
α
GTP
ATP
Active
adenylyl
cyclase
cAMP + PPi
Protein
kinase
(PKA)
Protein
phosphorylation
C
Hormone or neuro-
transmitter
Receptor
β
γ
α
Gq protein
Phospho-
lipase C
Diacylglycerol
Inositol
trisphosphate
Protein
phosphorylation
Calcium release
Protein kinase (PKC)

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Figure 3.10 Three mechanisms whereby binding of a neurotransmitter leads to a cellular effect.**A.** Receptors coupled to ion channels (ionotropic receptors). **B**. Receptors coupled to adenylyl cyclase (metabotropic receptors). **C**. Receptors coupled to diacylglycerol and inositol trisphosphate (metabotropic receptors).

Chapter Summary

- The major efferent components of autonomic nervous system (ANS) are the sympathetic nervous system (SNS) and parasympathetic nervous system (PSNS).
- The SNS and PSNS innervate major organs and organ systems in the body such as the heart, lungs, eyes, liver, kidney, circulatory system, gastrointestinal system, and urogenital system.
- The major effects of SNS activation are increase in blood pressure, dilation of pupils, decrease in activity of the gastrointestinal system, reduction in secretions, dilation of bronchial smooth muscles, and decrease in urinary frequency.
- The effects of the SNS are mediated by two major neurotransmitters, epinephrine and norepinephrine; the former is released from the adrenal medulla, whereas the latter is released by sympathetic neurons.
- The SNS is widely distributed, innervating practically all effector systems in the body. The sympathetic preganglionic fibers have a much broader influence than the parasympathetic fibers and synapse with a larger number of postganglionic neurons. This type of organization permits a diffuse discharge of the SNS.
- The parasympathetic division is more circumscribed than the SNS, with mostly one-to-few interactions, and the ganglia are also close to, or within, organs they innervate.
- The major effects of PSNS activation are almost opposite to that of SNS activation such as decrease in blood pressure, constriction of pupils, increase in activity of the gastrointestinal system, increase in secretions, constriction of bronchial smooth muscles, and increase in urinary frequency.
- The effects of the PSNS are mediated by acetylcholine released by cholinergic neurons.
- Acetylcholine produces its physiological effects by acting on muscarinic and/or nicotinic cholinergic receptors.

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STUDY QUESTIONS

Choose the ONE best answer.

3.1 Acetylcholine is the neurotransmitter that mediates contraction of skeletal muscles. Which of the following autonomic receptor types does acetylcholine bind to on the skeletal muscle cell to mediate muscle contraction?

A. Nicotinic
B. Muscarinic
C. Alpha-1
D. Beta-1

Correct answer = A. Skeletal muscle cells have nicotinic, not muscarinic, cholinergic receptors (see Figure 3.9), and motor neurons release acetylcholine at the neuromuscular junction that binds to the nicotinic receptors and causes muscle contraction. Acetylcholine does not bind to alpha-1 or beta-1 receptors that are adrenergic.

3.2 Which of the following physiologic changes occurs when the parasympathetic nervous system is activated?

A. Increase in heart rate
B. Inhibition of lacrimation (tears)
C. Dilation of the pupil (mydriasis)
D. Increase in gastric motility

Correct answer = D. Activation of the parasympathetic nervous system causes an increase in gastric motility, increase in fluid secretions, reduction in heart rate, and constriction of the pupil. In the “rest-and-digest” mode, the parasympathetic system is more active, which helps with digestion.

3.3 Which physiologic change is expected when the sympathetic nervous system is inhibited using a pharmacologic

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agent?

A. Reduction in heart rate
B. Increase in blood pressure
C. Decrease in fluid secretions
D. Constriction of blood vessels

Correct answer = A. Activation of the sympathetic nervous system causes an increase in heart rate, increase in blood pressure, reduction or thickening of fluid secretions, and constriction of blood vessels. Therefore, inhibition of the sympathetic system should theoretically cause a reduction in heart rate, decrease in blood pressure, increase in fluid secretions, and relaxation of blood vessels.

3.4 Which of the following is correct regarding activation of receptors on the effector organs in the ANS?

A. Acetylcholine activates muscarinic receptors.
B. Acetylcholine activates adrenergic receptors.
C. Epinephrine activates nicotinic receptors.
D. Norepinephrine activates muscarinic receptors.

Correct answer = A. Acetylcholine is the neurotransmitter in the cholinergic system, and it activates both muscarinic and nicotinic cholinergic receptors, not adrenergic receptors. Norepinephrine and epinephrine activate adrenergic receptors, not muscarinic receptors.

3.5 Which of the following is correct regarding synaptic transmission?

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A. Neurotransmitters are released from the axon terminals of presynaptic neurons.
B. Arrival of an action potential in the postsynaptic cell triggers release of neurotransmitter.
C. Intracellular calcium levels drop in the axon terminals before the release of neurotransmitter.
D.

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Serotonin and dopamine are the primary neurotransmitters in the ANS.

Correct answer = A. Neurotransmitters are released from the axon terminals of presynaptic neurons, triggered by the arrival of an action potential in the axon terminal of the presynaptic neuron (not in the postsynaptic cell). When an action potential arrives at the axon terminal, calcium enters the cell and calcium levels increase, resulting in release of the neurotransmitter. The main neurotransmitters in the ANS are norepinephrine and acetylcholine.

3.6 The pharmacologic strategy to reduce blood pressure in a patient with hypertension is to reduce cardiac output and/or reduce the peripheral vascular resistance caused by vasoconstriction. Cardiac output is a function of heart rate and force of contraction. Which of the following strategies will help to reduce blood pressure in a patient?

A. Inhibit the effects of sympathetic nervous system on the heart
B. Enhance the effects of sympathetic nervous system on the heart
C. Inhibit the effects of parasympathetic nervous system on the blood vessels
D. Enhance the effects of sympathetic nervous system on the blood vessels

Correct answer = A. Inhibiting the effects of the SNS on the heart will reduce heart rate and reduce force of contraction, thus reducing cardiac output and blood pressure. Enhancing the effects of SNS on the heart will increase blood pressure. The PSNS has a relaxant effect on blood vessels, hence inhibiting the effects of PSNS will lead to an increase in blood pressure. SNS has a vasoconstrictive effect on blood vessels, hence enhancing the effects of SNS will lead to an increase in blood pressure.

3.7 Which of the following effects is mediated by activation of cholinergic postganglionic neurons?

A. Bronchodilation

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B. Reduction in gastric motility
C. Pupillary constriction
D. Relaxation of the detrusor muscle

Correct answer = C. Postganglionic parasympathetic neurons innervating the sphincter pupillae muscle are cholinergic and contraction results in miosis. Bronchodilation results from activation of the SNS and not the PSNS. Reduction of gastric motility results from activation of the SNS. Relaxation of the detrusor muscle results from activation of the SNS.

3.8 A 67-year-old man is evaluated by his physician after fainting. He reports feeling lightheaded and then losing consciousness while tying his necktie in preparation for a formal gathering. Clinical and electrophysiologic testing supports a diagnosis of carotid sinus syndrome. Compression of the carotid sinus in this scenario mostly likely resulted in which of the following autonomic responses?

A. Increased sympathetic outflow to the peripheral vasculature
B. Decreased parasympathetic outflow to the peripheral vasculature
C. Increased parasympathetic outflow to the heart
D. Increased sympathetic outflow to the heart

Correct answer = C. Compression of the carotid sinus results in an increase in the frequency of firing of baroreceptor afferents traveling in the carotid sinus nerve, a branch of the glossopharyneal nerve. These afferents target the caudal (cardiorespiratory) portion of the solitary nucleus within the medulla. The solitary nucleus will activate cardiovagal efferents and in conjunction with medullary reticular centers decrease output from the intermediolateral cell column to postganglionic sympathetic neurons innervating the heart and smooth muscle of the peripheral vasculature. The resultant decrease in cardiac output and systemic vascular resistance produces a drop in blood pressure. See Figure 3.6. Note that the response in this case is opposite to that described in the figure.

3.9 Neurotransmitter binding to receptors on postganglionic neurons in autonomic ganglia results in which of the following?

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A. Cation influx through an intrinsic ion channel
B. G protein–mediated activation of adenylyl cyclase
C. G protein–mediated activation of phospholipase C
D. G protein–mediated inhibition of adenylyl cyclase

Correct answer = A. Preganglionic autonomic neurons are cholinergic. Ganglionic nicotinic acetylcholine receptors are ligand-gated ion channel receptors and produce direct postsynaptic responses by allowing sodium and calcium ions (cations) to pass through an intrinsic, cation selective pore. Muscarinic acetylcholine receptors are G protein–coupled receptors that produce modulatory effects through activation of second messengers. See Figure 3.10.

3.10 Activation of the SNS during the fight or flight response results in release of epinephrine and norepinephrine from the adrenal medulla into the blood stream. These catecholamines travel through the blood stream to bind to adrenergic receptors in other parts of the body, for example, the sinoatrial (SA) node of the heart. Which of the following best characterizes the mode of communication between the chromaffin cells of the adrenal medulla and the cells of the SA node of the heart?

A. Paracrine
B. Direct contact
C. Endocrine
D. Synaptic

Correct answer = C. The chromaffin cells of the adrenal medulla release epinephrine and norepinephrine into the blood stream. Because the catecholamines travel through the blood stream to reach their target cells, this type of intercellular communication is best characterized as endocrine signaling. See Figure 3.8.

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4

Cholinergic Agonists

Rosemary A. Poku, Felix Amissah

I. OVERVIEW

Drugs affecting the autonomic nervous system (ANS) are divided into two groups according to the type of receptors involved in the mechanism of action. The cholinergic drugs, which are described in this chapter, and the anticholinergic drugs, described in Chapter 5, act on receptors activated by acetylcholine (ACh). The adrenergic drugs (Chapters 6 and 7) act on receptors stimulated by norepinephrine or epinephrine. Cholinergic and adrenergic drugs act by either stimulating or blocking receptors of the ANS. Figure 4.1 summarizes cholinergic agonists discussed in this chapter.

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DIRECT ACTING

Acetylcholine MIOCHOL-E
Bethanechol URECHOLINE
Carbachol MIOSTAT
Cevimeline EVOXAC
Methacholine PROVOCHOLINE
Nicotine NICORETTE
Pilocarpine SALAGEN, ISOPTO CARPINE

INDIRECT ACTING (reversible)

Donepezil ARICEPT
Edrophonium ENLON
Galantamine RAZADYNE
Neostigmine BLOXIVERZ
Physostigmine GENERIC ONLY
Pyridostigmine MESTINON
Rivastigmine EXELON

INDIRECT ACTING (irreversible)

Echothiophate PHOSPHOLINE IODIDE

REACTIVATION OF ACETYLCHOLINESTERASE

Pralidoxime PROTOPAM

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Figure 4.1 Summary of cholinergic agonists.

II. THE CHOLINERGIC NEURON

The preganglionic fibers terminating in the adrenal medulla, the autonomic ganglia (both parasympathetic and sympathetic), and the postganglionic fibers of the parasympathetic division use ACh as a neurotransmitter (Figure 4.2). The postganglionic sympathetic division of sweat glands also uses ACh. In addition, cholinergic neurons innervate the muscles of the somatic system and play an important role in the central nervous system (CNS).

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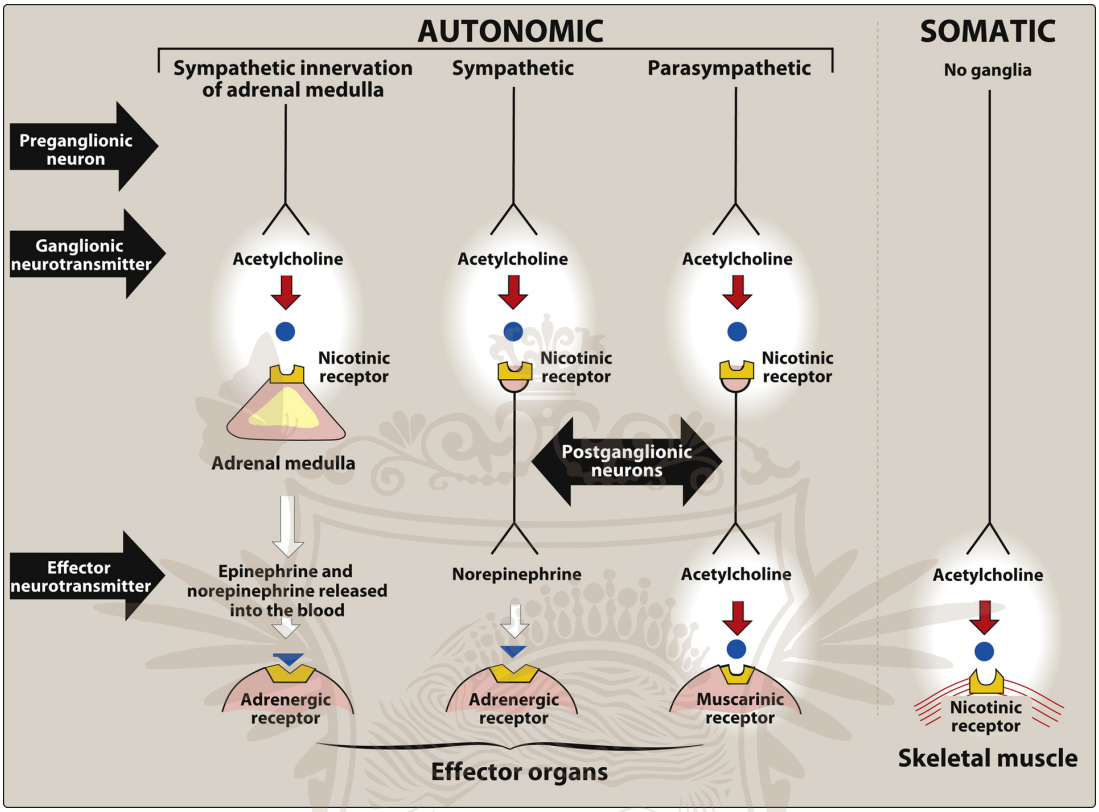

Figure 4.2 Sites of actions of cholinergic agonists in the autonomic and somatic nervous systems.

A. Neurotransmission at cholinergic neurons

Neurotransmission in cholinergic neurons involves six sequential steps: (1) synthesis of ACh, (2) storage, (3) release, (4) binding of ACh to the receptor, (5) degradation of ACh in the synaptic cleft (the space between the nerve endings and adjacent receptors on nerves or effector organs), and (6) recycling of choline (Figure 4.3).

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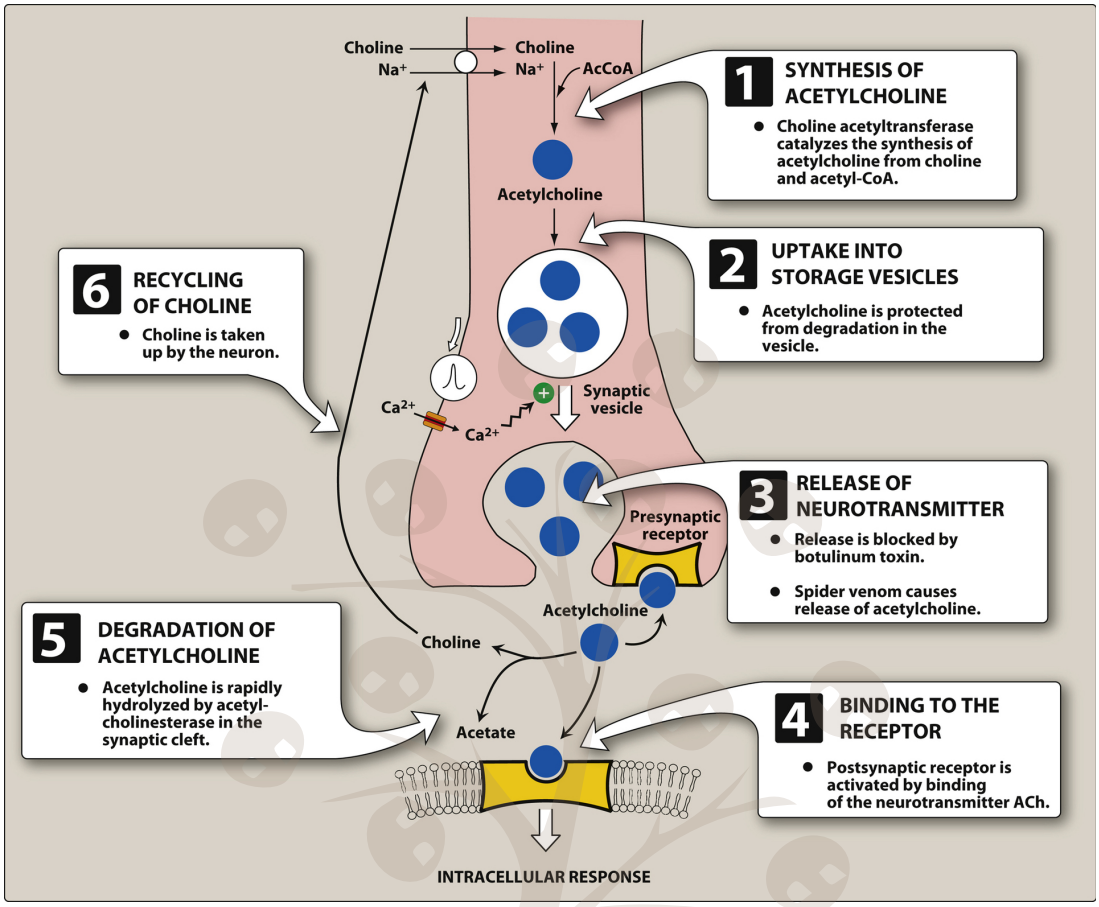

Figure 4.3 Synthesis and release of acetylcholine from the cholinergic neuron.AcCoA = acetyl coenzyme A.

1.Synthesis of acetylcholine: Choline is transported from the extracellular fluid into the cytoplasm of the cholinergic neuron by an energy-dependent carrier system that cotransports sodium. [Note: Choline has a quaternary nitrogen and carries a permanent positive charge and, thus, cannot diffuse through the membrane.] The uptake of choline is the rate-limiting step in ACh synthesis. Choline acetyltransferase catalyzes the reaction of choline with acetyl coenzyme A (CoA) to form ACh (an ester) in the cytosol.

2.Storage of acetylcholine in vesicles: ACh is packaged and stored into presynaptic vesicles by an active transport process. The mature vesicle contains not only ACh

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(the primary neurotransmitter) but also adenosine triphosphate (ATP), which is a cotransmitter and proteoglycan. Cotransmission from autonomic neurons is the rule rather than the exception. This means that most synaptic vesicles contain the primary neurotransmitter (here, ACh) as well as a cotransmitter (here, ATP).

3.Release of acetylcholine: When an action potential propagated by voltage-sensitive sodium channels arrives at a nerve ending, voltage-sensitive calcium channels on the presynaptic membrane open, causing an increase in the concentration of intracellular calcium. Elevated calcium levels promote the fusion of synaptic vesicles with the presynaptic membrane and the release of vesicular contents into the synaptic space. This release can be blocked by botulinum toxin. In contrast, the toxin in black widow spider venom causes all the ACh stored in synaptic vesicles to empty into the synaptic gap.

4.Binding to the receptor: ACh released from the synaptic vesicles diffuses across the synaptic space and binds to postsynaptic receptors on the target cell, to presynaptic receptors on the membrane of the neuron that released ACh, or to other targeted presynaptic receptors. The postsynaptic cholinergic receptors on the surface of effector organs are divided into two classes: muscarinic and nicotinic (Figure 4.2). Binding to a receptor leads to a biologic response within the cell, such as the initiation of a nerve impulse in a postganglionic fiber or activation of specific enzymes in effector cells, as mediated by secondary messengers.

5.Degradation of acetylcholine: The signal at the postjunctional effector site is rapidly terminated, because acetylcholinesterase (AChE) cleaves ACh to choline and acetate in the synaptic cleft.

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6.Recycling of choline: Choline may be recaptured by a sodium-coupled, high-affinity uptake system that transports the molecule back into the neuron. There, it is available to be acetylated into ACh.

III. CHOLINERGIC RECEPTORS (CHOLINOCEPTORS)

Two families of cholinoceptors, designated muscarinic and nicotinic receptors, can be distinguished from each other on the basis of their different affinities for agents that mimic the action of ACh (cholinomimetic agents).

A. Muscarinic receptors

Muscarinic receptors belong to the class of G protein–coupled receptors (metabotropic receptors). These receptors, in addition to binding ACh, also recognize muscarine, an alkaloid in certain poisonous mushrooms. By contrast, the muscarinic receptors show only a weak affinity for *nicotine*, an alkaloid found in tobacco and other plants (Figure 4.4A). There are five subclasses of muscarinic receptors; however, only M_1, M_2, and M_3 receptors have been functionally characterized.

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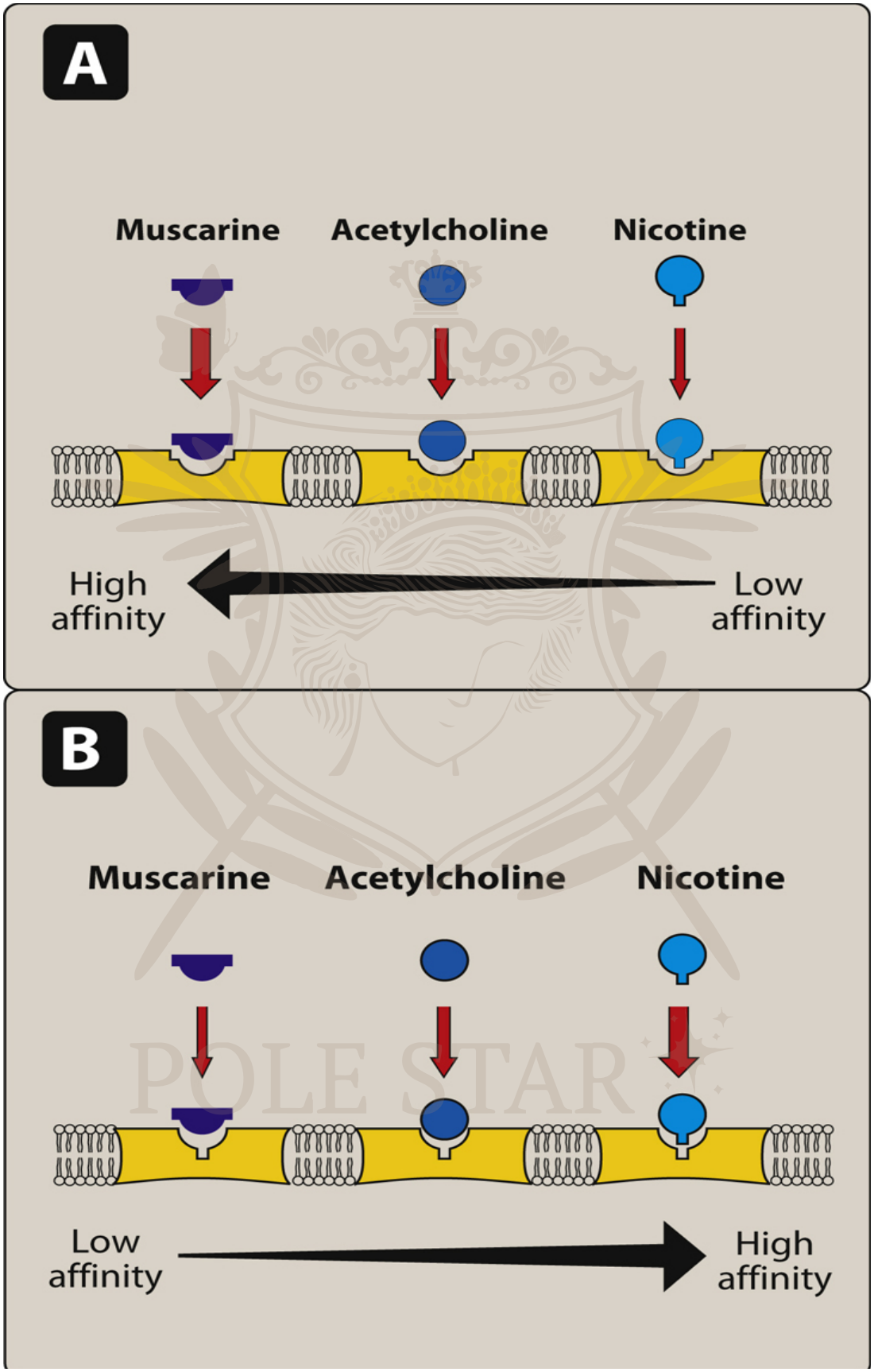
A
Muscarine
Acetylcholine
Nicotine
High affinity
Low affinity
B
Muscarine
Acetylcholine
Nicotine
Low affinity
High affinity

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Figure 4.4 Types of cholinergic receptors.**A**. Muscarinic receptors. **B.** Nicotinic receptors.

1.Location of muscarinic receptors: These receptors are found on the autonomic effector organs, such as the heart, smooth muscle, brain, and exocrine glands. Although all five subtypes are found on neurons, M_1 receptors are also found on gastric parietal cells, M_2 receptors on cardiac cells and smooth muscle, and M_3 receptors on the lung, bladder, exocrine glands, and smooth muscle. [Note: Drugs with muscarinic actions preferentially stimulate muscarinic receptors on these tissues, but at high concentration, they may show some activity at nicotinic receptors.]

2.Mechanism of acetylcholine signal transduction: A number of different molecular mechanisms transmit the signal generated by ACh occupation of the receptor. For example, when M_1 or M_3 receptors are activated, the receptor undergoes a conformational change and interacts with a G protein that activates phospholipase C. This ultimately leads to production of second messengers inositol-1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 causes an increase in intracellular Ca^{2+}, which allows calcium to either stimulate or inhibit enzymes or to cause hyperpolarization, secretion, or contraction. DAG activates protein kinase C, an enzyme that phosphorylates numerous proteins within the cell. In contrast, activation of the M_2 subtype on the cardiac muscle stimulates a G protein that inhibits adenylyl cyclase and increases K^+ conductance. Subsequently, the heart responds by decreasing both the rate and force of contraction.

3.Muscarinic agonists: Muscarinic agonists may act directly by binding and activating the muscarinic receptors

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(see Section IV) or indirectly by inhibiting acetylcholinesterase (AChE), which breaks down ACh (see Section V).

B. Nicotinic receptors

These receptors, in addition to binding ACh, also recognize *nicotine* but show only a weak affinity for muscarine (Figure 4.4B). The nicotinic receptor is composed of five subunits, and it functions as a ligand-gated ion channel (ionotropic receptor). Binding of two ACh molecules elicits a conformational change that allows the entry of sodium ions, resulting in the depolarization of the effector cell. *Nicotine* at low concentration stimulates the receptor, whereas *nicotine* at high concentration blocks the receptor. Nicotinic receptors are located in the CNS, the adrenal medulla, autonomic ganglia, and the neuromuscular junction (NMJ) in skeletal muscles. Those at the NMJ are sometimes designated N_M, and the others, N_N. The nicotinic receptors of autonomic ganglia differ from those of the NMJ. For example, ganglionic receptors are selectively blocked by *mecamylamine*, whereas NMJ receptors are specifically blocked by neuromuscular blocking drugs like *atracurium*.

IV. DIRECT-ACTING CHOLINERGIC AGONISTS

Cholinergic agonists mimic the effects of ACh by binding directly to cholinoceptors (muscarinic or nicotinic). These agents may be broadly classified into two groups: (1) choline esters, which include endogenous ACh and synthetic esters of choline, such as *carbachol* and *bethanechol*, and (2) naturally occurring alkaloids, such as *nicotine* and *pilocarpine* (Figure 4.5) and their synthetic analogs (*cevimeline*). All direct-acting cholinergic drugs have a longer duration of action than ACh. The therapeutically useful drugs (*pilocarpine* and *bethanechol*) preferentially bind to muscarinic receptors and are referred to as muscarinic agents. However, as a

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group, the direct-acting agonists manifest poor specificity in their actions, which limits clinical usefulness.

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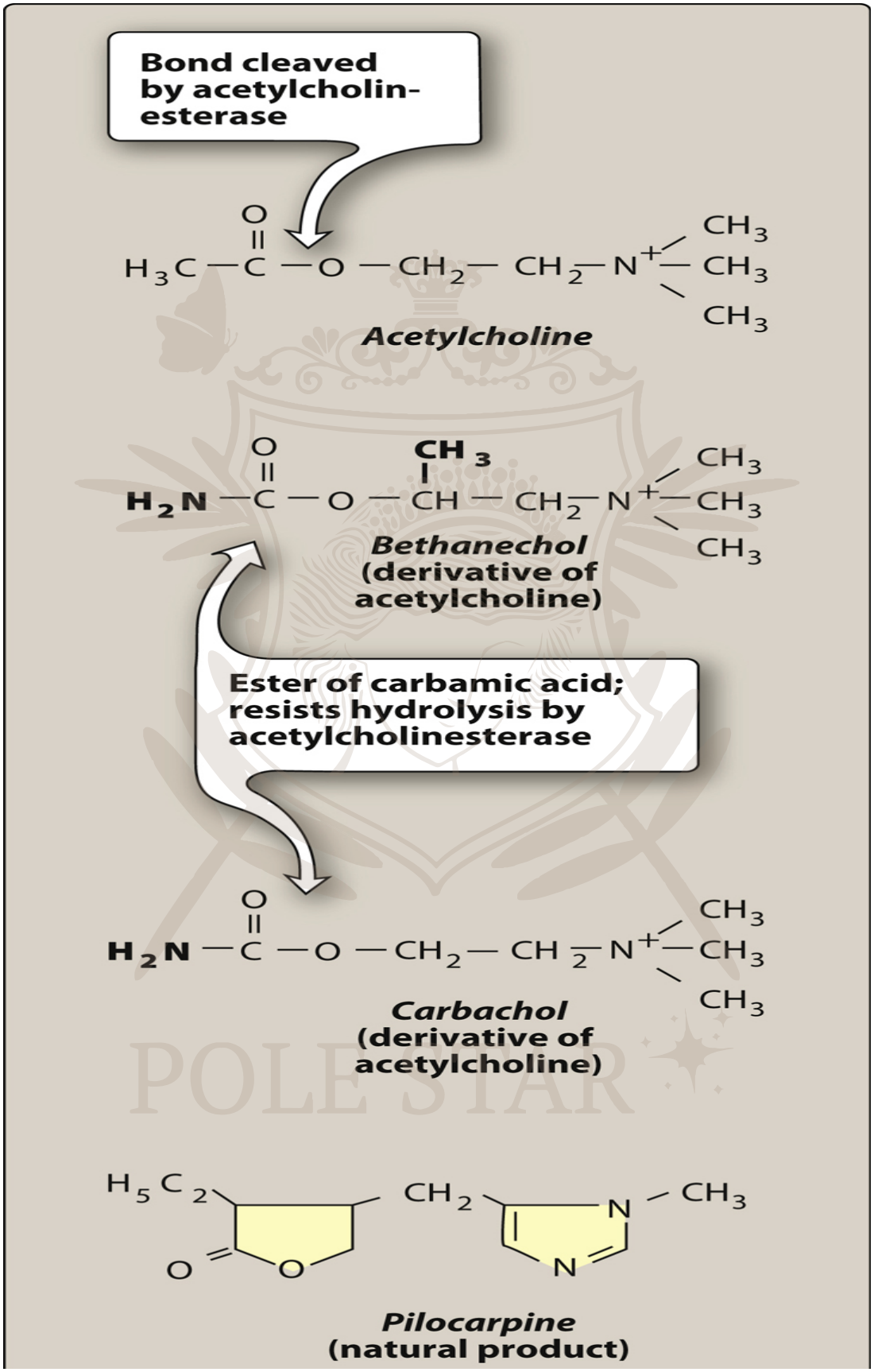

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Figure 4.5 Comparison of the structures of some cholinergic agonists.

A. Acetylcholine

Acetylcholine [ah-see-teel-KOE-leen] is a quaternary ammonium compound that cannot penetrate membranes because of its positive charge. Although it is the neurotransmitter of parasympathetic and somatic nerves as well as autonomic ganglia, it lacks therapeutic importance because of its multiplicity of actions (leading to diffuse effects) and its rapid inactivation by the cholinesterases. ACh maintains both muscarinic and nicotinic activity. Its actions include the following:

1. **Decrease in heart rate and cardiac output:** The actions of ACh on the heart mimic the effects of vagal stimulation. For example, if injected intravenously, ACh acts on M_2 receptors to produce a brief decrease in cardiac rate (bradycardia) and, subsequently, cardiac output resulting from a reduction in the rate of firing at the sinoatrial (SA) node. [Note: Normal vagal activity regulates the heart by the release of ACh at the SA node.]

2. **Decrease in blood pressure:** Injection of ACh causes vasodilation and lowering of blood pressure by an indirect mechanism of action. ACh activates M_3 receptors found on endothelial cells lining the smooth muscles of blood vessels. This results in the production of nitric oxide from arginine. Nitric oxide then diffuses to vascular smooth muscle cells to stimulate protein kinase G production, leading to hyperpolarization and smooth muscle relaxation via phosphodiesterase-3 inhibition. In the absence of administered cholinergic agents, the vascular cholinergic receptors have no known function, because ACh is never released into the blood in significant quantities. *Atropine* blocks these muscarinic receptors and prevents ACh from producing vasodilation.

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3.Other actions: In the gastrointestinal (GI) tract, acetylcholine increases salivary secretion, increases gastric acid secretion, and stimulates intestinal secretions and motility. It also enhances bronchiolar secretions and causes bronchoconstriction. [Note: *Methacholine*, a direct-acting cholinergic agonist, is used to assist in the diagnosis of asthma due to its bronchoconstricting properties.] In the genitourinary tract, ACh increases the tone of the detrusor muscle, causing urination. In the eye, ACh is involved in stimulation of ciliary muscle contraction for near vision and in the constriction of the pupillae sphincter muscle, causing miosis (marked constriction of the pupil). ACh (1% solution) is instilled into the anterior chamber of the eye to produce miosis during ophthalmic surgery.

B. Bethanechol

Bethanechol [be-THAN-e-kole] is an unsubstituted carbamoyl ester, structurally related to ACh (see Figure 4.5). It is not hydrolyzed by AChE due to the esterification of carbamic acid, although it is inactivated through hydrolysis by other esterases. It lacks nicotinic actions (due to addition of the methyl group) but does have strong muscarinic activity. Its major actions are on the smooth musculature of the bladder and GI tract. It has about a 1-hour duration of action.

1.Actions: *Bethanechol* directly stimulates muscarinic receptors, causing increased intestinal motility and tone. It also stimulates the detrusor muscle of the bladder, whereas the trigone and sphincter muscles are relaxed. These effects stimulate urination.

2.Therapeutic uses: In urologic treatment, *bethanechol* is used to stimulate the atonic bladder, particularly in postpartum or postoperative, nonobstructive urinary retention. *Bethanechol* may also be used to treat neurogenic atony as manifested in clinical pathology such as toxic megacolon.

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3.Adverse effects: *Bethanechol* can cause generalized cholinergic stimulation (Figure 4.6), with sweating, salivation, flushing, decreased blood pressure (with reflex tachycardia), nausea, abdominal pain, diarrhea, and bronchospasm. *Atropine sulfate* may be administered to overcome severe cardiovascular or bronchoconstrictor responses to this agent.

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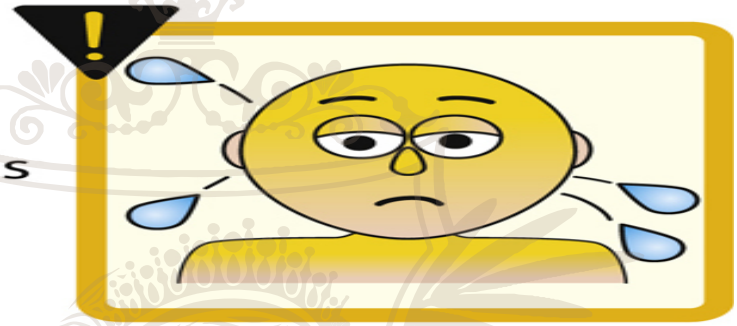
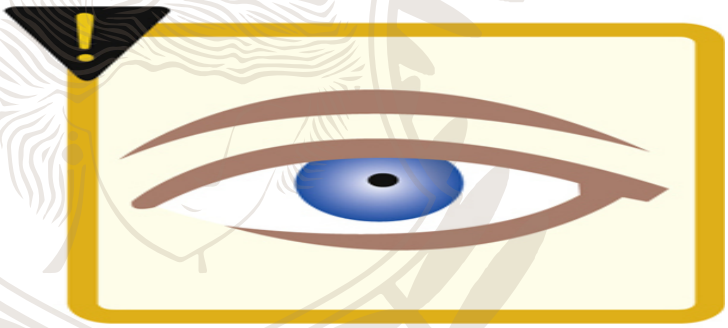
Diarrhea

Diaphoresis



Miosis



Nausea

Urinary urgency

POLE STAR

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Figure 4.6 Some adverse effects with cholinergic agonists.

C. Carbachol (carbamylcholine)

Carbachol [KAR-ba-kole] has both muscarinic and nicotinic actions. Like *bethanechol*, *carbachol* is an ester of carbamic acid (see Figure 4.5) and a poor substrate for AChE. It is biotransformed by other esterases, but at a much slower rate.

1. Actions: *Carbachol* has profound effects on both the cardiovascular and GI systems because of its ganglion-stimulating activity, and it may first stimulate and then depress these systems. It can cause release of epinephrine from the adrenal medulla by its nicotinic action. Locally instilled into the eye, it mimics the effects of ACh, causing miosis and a spasm of accommodation in which the ciliary muscle of the eye remains in a constant state of contraction. The vision becomes fixed at some particular distance, making it impossible to focus (Figure 4.7). [Note the opposing effects of *atropine*, a muscarinic blocker, on the eye.]

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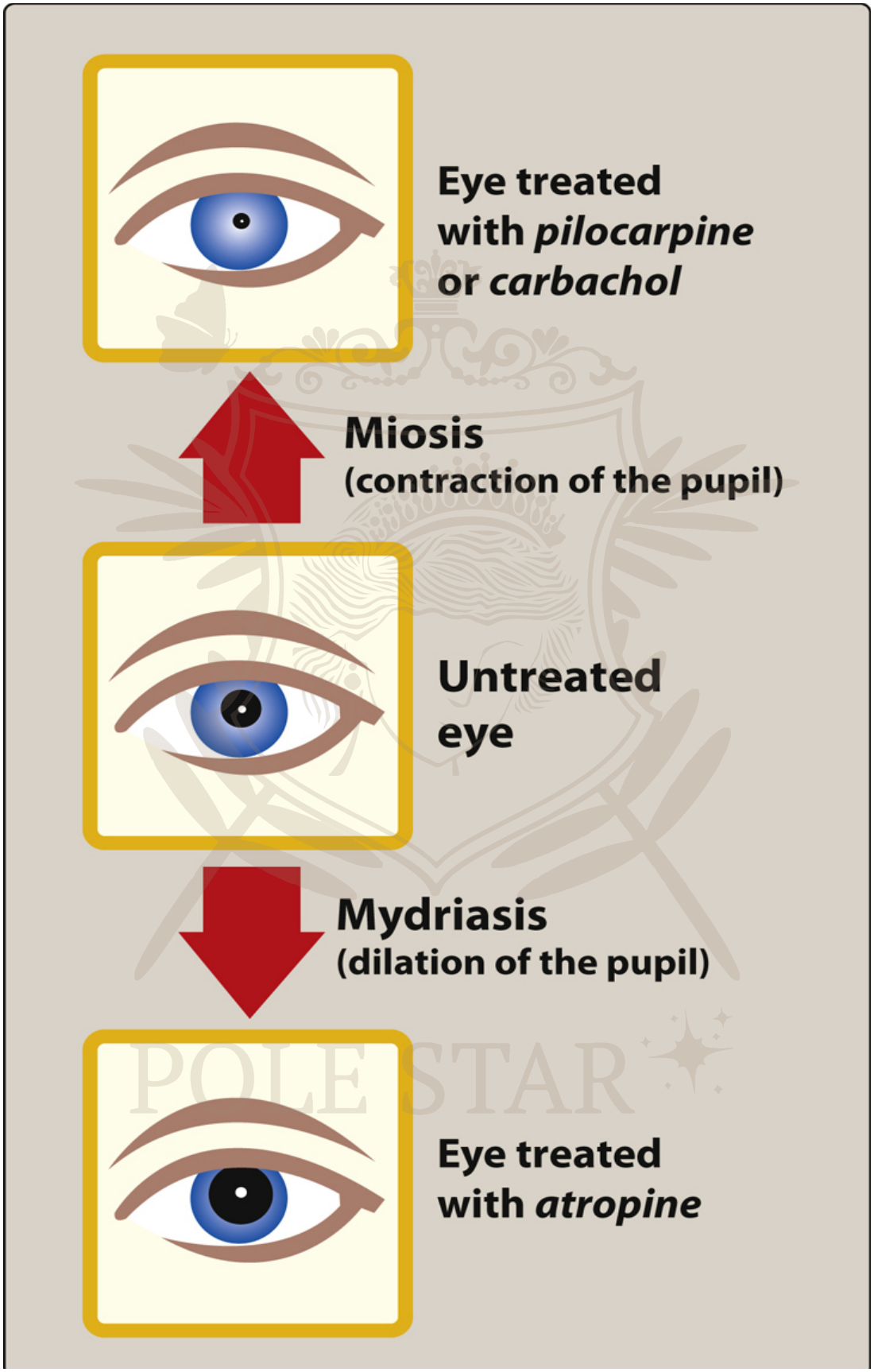
Eye treated with *pilocarpine* or *carbachol*
Miosis
(contraction of the pupil)
Untreated eye
Mydriasis
(dilation of the pupil)
Eye treated with *atropine*

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Figure 4.7 Actions of *pilocarpine*, *carbachol*, and *atropine* on the iris and ciliary muscle of the eye.

2.Therapeutic uses: Because of its high potency, receptor nonselectivity, and relatively long duration of action, *carbachol* is rarely used. Intraocular use provides miosis for eye surgery and lowers intraocular pressure in the treatment of glaucoma.

3.Adverse effects: With ophthalmologic use, few adverse effects occur due to lack of systemic absorption (quaternary amine—positively charged).

D. Pilocarpine

The alkaloid *pilocarpine* [pye-loe-KAR-peen] is a tertiary amine and does not undergo hydrolysis by AChE (see Figure 4.5). Compared with ACh and its derivatives, it is far less potent but is uncharged and can penetrate the CNS at therapeutic doses. *Pilocarpine* exhibits muscarinic activity and is used primarily in ophthalmology.

1.Actions: Applied topically to the eye, *pilocarpine* produces rapid miosis, contraction of the ciliary muscle, and spasm of accommodation. *Pilocarpine* is one of the most potent stimulators of secretions such as sweat, tears, and saliva, but its use for producing these effects has been limited due to its lack of selectivity.

2.Therapeutic uses: *Pilocarpine* is used to treat glaucoma and is the drug of choice to reduce intraocular pressure emergently for both open-angle and angle-closure glaucoma. *Pilocarpine* is extremely effective in opening the trabecular meshwork around the Schlemm canal, causing an immediate drop in intraocular pressure because of the increased drainage of aqueous humor. This action occurs within a few minutes, lasts 4 to 8 hours, and can be repeated. [Note: Topical

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carbonic anhydrase inhibitors, such as *dorzolamide* and β-adrenergic blockers such as *timolol*, are effective in treating glaucoma but are not used to reduce intraocular pressure emergently.] The miotic action of *pilocarpine* is also useful in reversing mydriasis due to *atropine* administration.

Pilocarpine facilitates salivation in patients with xerostomia resulting from irradiation of the head and neck. Sjögren syndrome, which is characterized by dry mouth and lack of tears, is treated with oral *pilocarpine* tablets or *cevimeline*, a cholinergic drug that also has the drawback of being nonspecific.

3.Adverse effects: *Pilocarpine* can cause blurred vision, night blindness, and brow ache. Poisoning with this agent is characterized by exaggeration of various parasympathetic effects, including profuse sweating (diaphoresis) and salivation. The effects are similar to those produced by consumption of mushrooms of the genus *Inocybe*, which contain muscarine. Parenteral *atropine*, at doses high enough to cross the blood–brain barrier, is administered to counteract the toxicity of *pilocarpine*.

V. INDIRECT-ACTING CHOLINERGIC AGONISTS: ANTICHOLINESTERASE AGENTS (REVERSIBLE)

AChE is an enzyme that specifically cleaves ACh to acetate and choline and, thus, terminates its actions. It is located both pre- and postsynaptically in the nerve terminal where it is membrane bound. Inhibitors of AChE (anticholinesterase agents or cholinesterase inhibitors) indirectly enhance cholinergic action by preventing the degradation of ACh. This results in accumulation of ACh in the synaptic space (Figure 4.8). Therefore, these drugs can provoke a response at all cholinoceptors, including both muscarinic and

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nicotinic receptors of the ANS, as well as at the NMJ and in the brain. The reversible AChE inhibitors can be broadly classified as either short-acting or intermediate-acting agents.

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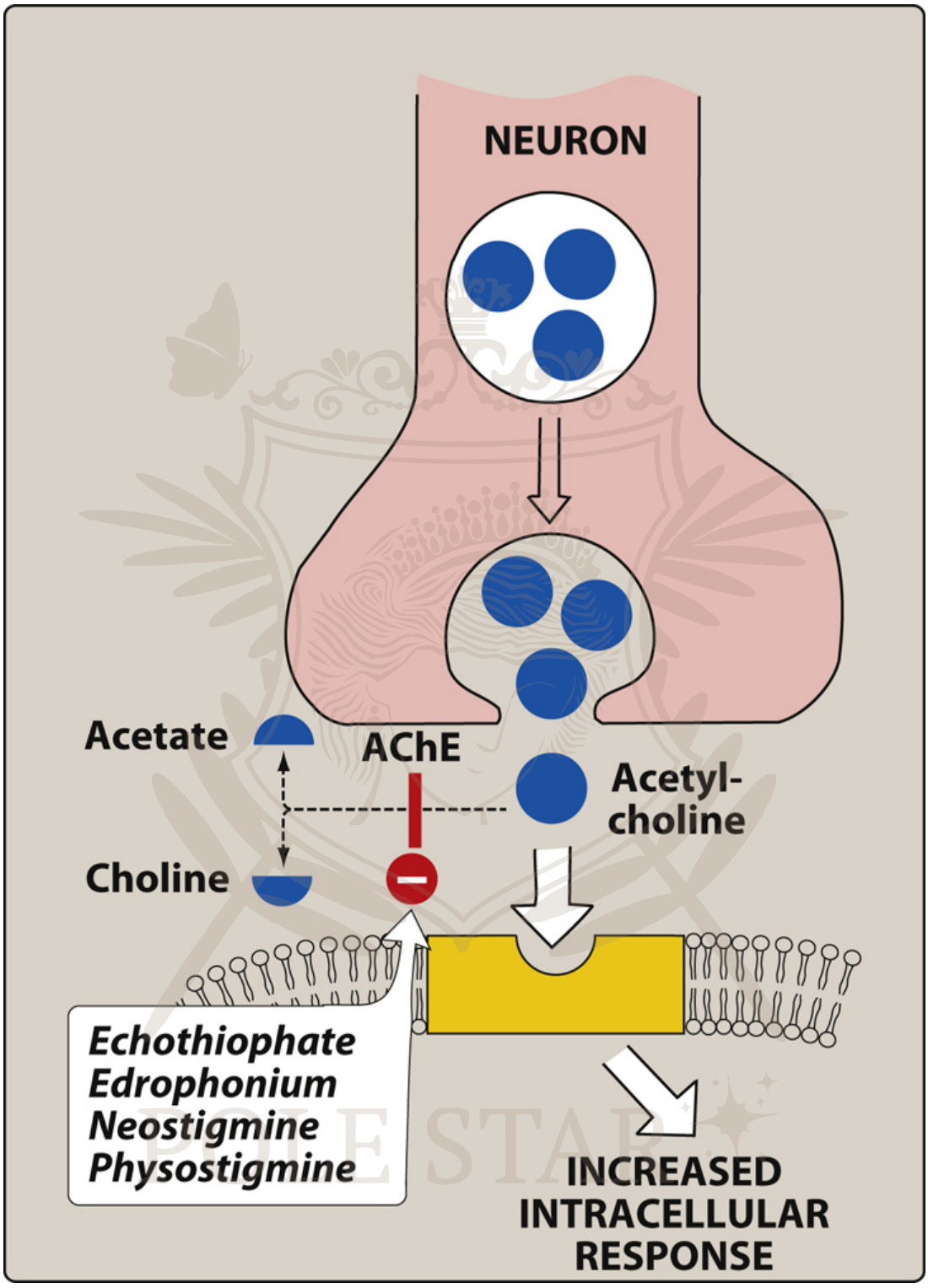

Figure 4.8 Mechanisms of action of indirect cholinergic agonists.AChE = acetylcholinesterase.

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A. Edrophonium

Edrophonium [ed-row-FOE-nee-um] is the prototype short-acting AChE inhibitor. *Edrophonium* binds reversibly to the active center of AChE, preventing hydrolysis of ACh. It has a short duration of action of 10 to 20 minutes due to rapid renal elimination. *Edrophonium* is a quaternary amine, and its actions are limited to the periphery because its polarity prevents crossing the blood–brain barrier. Historically *edrophonium* was used in the diagnosis of myasthenia gravis, an autoimmune disease caused by antibodies to the nicotinic receptor at the NMJ. In myasthenia gravis, degradation of the nicotinic receptors results in fewer receptors available for interaction with ACh. Intravenous injection of *edrophonium* leads to a rapid increase in muscle strength in patients with myasthenia gravis by increasing the local amounts of ACh available to bind to the NMJ. Due to the availability of other agents and improved diagnostic techniques for myasthenia gravis (for example, blood tests for antibodies to the ACh receptor), *edrophonium* has been removed from the market.

B. Physostigmine

Physostigmine [fi-zoe-STIG-meen] is a nitrogenous carbamic acid ester found naturally in plants and is a tertiary amine. It is a substrate for AChE, and it forms a relatively stable carbamoylated intermediate with the enzyme, which then becomes reversibly inactivated. The result is potentiation of cholinergic activity throughout the body.

1. **Actions:** *Physostigmine* has a wide range of effects and stimulates not only the muscarinic and nicotinic sites of the ANS but also the nicotinic receptors of the NMJ. Muscarinic stimulation can cause contraction of GI smooth muscles, miosis, bradycardia, and hypotension (Figure 4.9). Nicotinic stimulation can cause skeletal muscle twitches, fasciculations, and skeletal muscle paralysis (at higher doses). Its duration of action is about 30 minutes to 2 hours, and it is considered an

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intermediate-acting agent. The tertiary amine structure permits *physostigmine* to enter and stimulate the cholinergic sites in the CNS.

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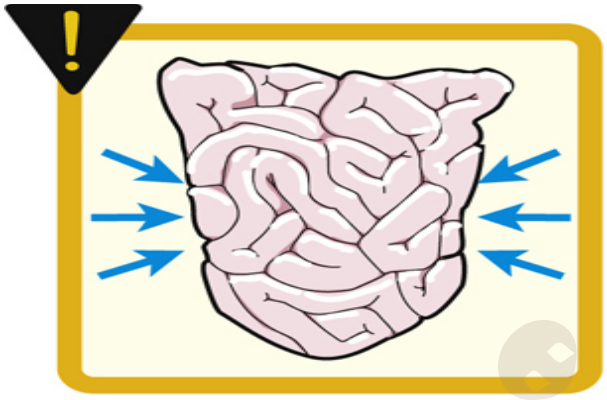
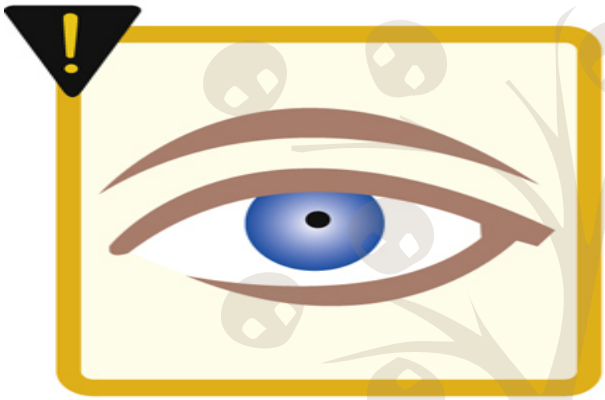
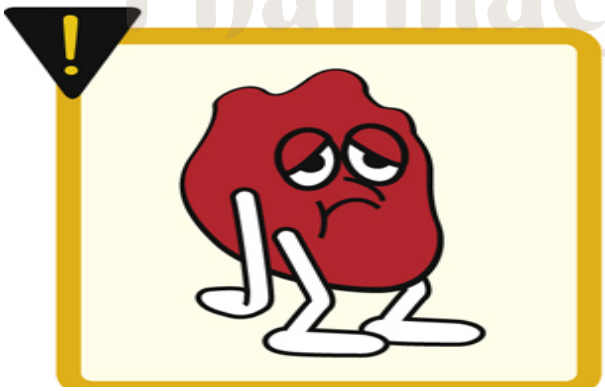


Contraction of visceral smooth muscle



Miosis

Hypotension



Bradycardia

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Figure 4.9 Some actions of *physostigmine*.

2.Therapeutic uses: *Physostigmine* is used in the treatment of overdoses of drugs with anticholinergic actions, such as *atropine.* Due to its ability to enter the CNS, it is able to reverse the unwanted CNS effects of anticholinergics.

3.Adverse effects: High doses of *physostigmine* may lead to convulsions. Bradycardia and a decrease in cardiac output may also occur. Inhibition of AChE at the NMJ leads to the accumulation of ACh, and theoretically, the resulting continuous NMJ depolarization may result in paralysis of skeletal muscle. However, these effects are rarely seen with therapeutic doses.

C. Neostigmine

Neostigmine [nee-oh-STIG-meen] is a synthetic compound that is also a carbamic acid ester, and it reversibly inhibits AChE in a manner similar to *physostigmine*.

1.Actions: Unlike *physostigmine*, *neostigmine* has a quaternary nitrogen. Therefore, it is more polar, poorly absorbed from the GI tract, and unable to enter the CNS. Its effect on skeletal muscle is greater than *physostigmine*, and it can stimulate contractility before paralyzing any muscular activity. *Neostigmine* has an intermediate duration of action, usually 30 minutes to 2 hours.

2.Therapeutic uses: It is used to stimulate the bladder and GI tract and as a reversal agent for the paralytic activity of competitive neuromuscular-blocking agents. *Neostigmine* is also used to manage symptoms of myasthenia gravis.

3.Adverse effects: Adverse effects of *neostigmine* include those of generalized cholinergic stimulation, such as salivation, flushing, decreased blood pressure, nausea,

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abdominal pain, diarrhea, and bronchospasm. *Neostigmine* does not cause CNS side effects and is not used to overcome toxicity of central-acting antimuscarinic agents such as *atropine. Neostigmine* is contraindicated when intestinal or urinary bladder obstruction is present.

D. Pyridostigmine

Pyridostigmine [peer-id-oh-STIG-meen] is another cholinesterase inhibitor used in the chronic management of myasthenia gravis. Its duration of action is intermediate (3-6 hours) but longer than that of *neostigmine.* Adverse effects are similar to those of *neostigmine*.

E. Tacrine, donepezil, rivastigmine, and galantamine

Patients with Alzheimer disease (AD) have a deficiency of cholinergic neurons, and therefore, lower levels of ACh are present in the CNS. This observation led to the development of anticholinesterases as possible therapies for the deterioration of cognitive function. *Tacrine* [TAK-reen], the first agent in this category, has been replaced by others because of its hepatotoxicity. Despite the ability of *donepezil* [doe-NEP-e-zil], *rivastigmine* [ri-va-STIG-meen], and *galantamine* [ga-LAN-ta-meen] to delay the progression of AD, none can stop its progression. GI distress is their primary adverse effect (see Chapter 15).

Clinical Application 4.1: Cholinesterase Inhibitors Used in Alzheimer Disease

The management of Alzheimer disease (AD) is challenging due to the absence of a robust pharmacologic treatment. The key focus of pharmacotherapy for AD is improving areas of cognition, neuropsychiatric symptoms, and functional ability. Cholinesterase inhibitors are useful in the treatment of cognitive symptoms of AD. They produce modest improvements in cognitive, global, and functional outcomes in people with mild to moderate AD. The duration of benefit varies from 3 to 24 months. Tacrine, the first anticholinesterase recommended for AD, is no longer used due to hepatotoxicity. It has been largely replaced with

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newer cholinesterase inhibitors that are relatively safer and more tolerable, such as donepezil, rivastigmine, and galantamine. For each of these drugs, the dose must be increased gradually over 4 to 6 weeks to minimize potential side effects. Although the specific mechanism of cholinesterase inhibitory action differs slightly between drugs in this class, the clinical importance of these differences is not apparent. The ease of use, patient preference, cost and safety issues, and pharmacokinetic properties largely determine the choice of cholinesterase inhibitor for individual patients. For instance, if treatment with agents with short half-lives such as rivastigmine (1.5 hours) and galantamine (7 hours) is interrupted for several days or longer, the patient should be restarted at the lowest dose and titrated to the current dose. This is not true of donepezil, which has a half-life of 70 hours. The combination of cholinesterase inhibitors with memantine (N-methyl-D-aspartate glutamate antagonist) in moderate to severe AD has been shown to improve functional ability with a decreased rate of cognitive deterioration.

VI. INDIRECT-ACTING CHOLINERGIC AGONISTS: ANTICHOLINESTERASE AGENTS (IRREVERSIBLE)

A number of synthetic organophosphate compounds have the ability to bind covalently to AChE. The result is a long-lasting increase in ACh at all sites where it is released. Many of these drugs are extremely toxic and were developed by the military as nerve agents for chemical warfare. Related compounds, such as *parathion* and *malathion*, are used as insecticides.

A. Echothiophate

1. Mechanism of action: *Echothiophate* [ek-oe-THI-oh-fate] is an organophosphate that covalently binds via its phosphate group at the active site of AChE (Figure 4.10). Once this occurs, the enzyme is permanently inactivated, and restoration of AChE activity requires the synthesis of new enzyme molecules. Following covalent modification of AChE, the phosphorylated enzyme slowly releases one of its ethyl

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groups. The loss of an alkyl group, which is called “aging,” makes it impossible for chemical reactivators, such as *pralidoxime*, to break the bond between the remaining drug and the enzyme.

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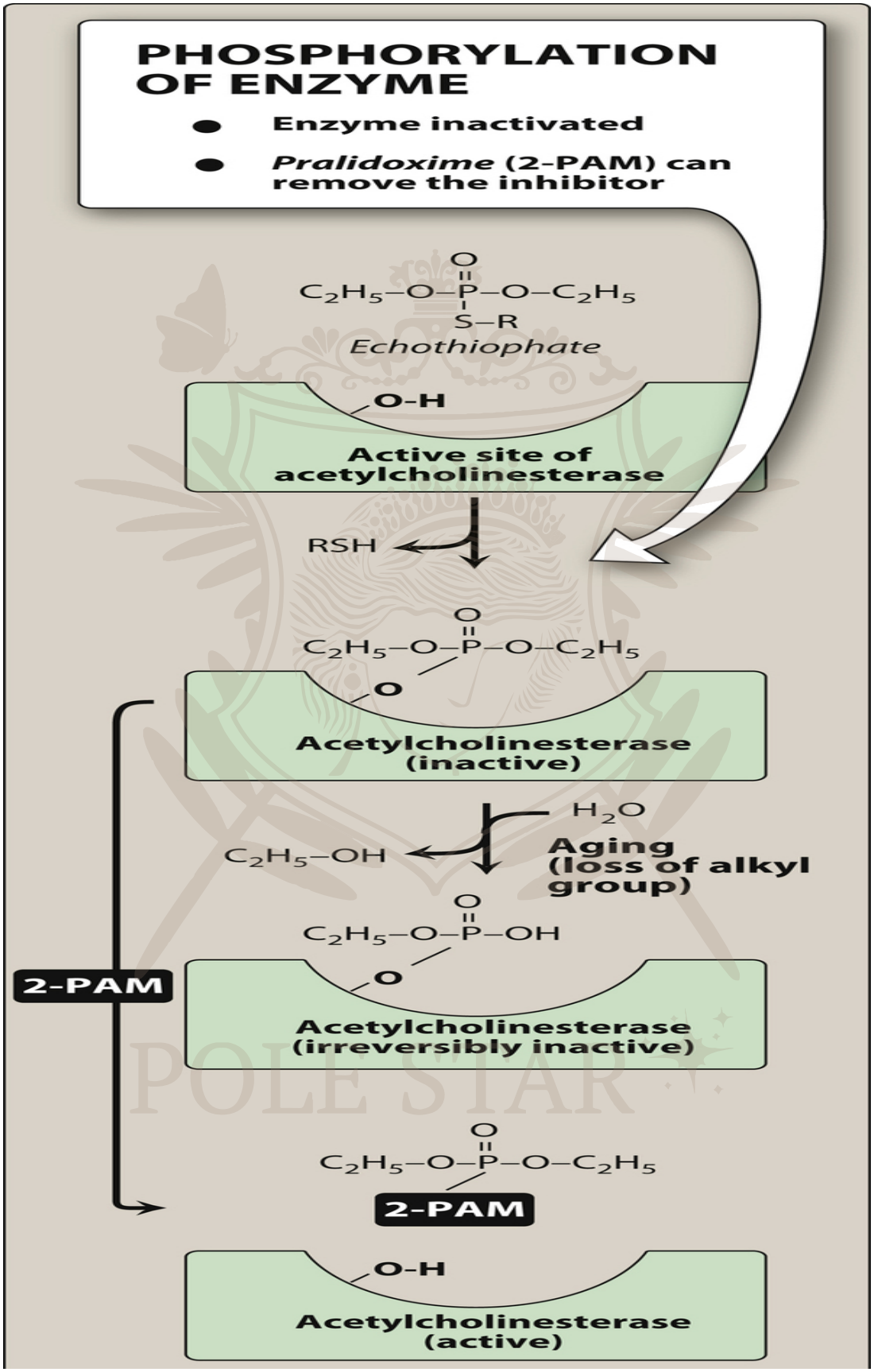
PHOSPHORYLATION OF ENZYME
Enzyme inactivated
Pralidoxime (2-PAM) can remove the inhibitor
C2H5–O–P(=O)(S–R)–O–C2H5
Echothiophate
O-H
Active site of acetylcholinesterase
RSH
C2H5–O–P(=O)(O)–O–C2H5
Acetylcholinesterase (inactive)
H2O
C2H5–OH
Aging (loss of alkyl group)
C2H5–O–P(=O)(OH)–O
Acetylcholinesterase (irreversibly inactive)
2-PAM
C2H5–O–P(=O)–O–C2H5
2-PAM
O-H
Acetylcholinesterase (active)

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Figure 4.10 Covalent modification of acetylcholinesterase by *echothiophate*.Also shown is the reactivation of the enzyme with *pralidoxime* (2-PAM). R = $(CH_3)_3N^+–CH_2–CH_2–$; RSH = $(CH_3)_3N^+–CH_2–CH_2–S$-H.

2.Actions: Actions include generalized cholinergic stimulation, paralysis of motor function (causing breathing difficulties), and convulsions. *Echothiophate* produces intense miosis and intraocular pressure falls from the facilitation of outflow of aqueous humor. *Atropine* in high dosages can reverse many of the peripheral and some of the central muscarinic effects of *echothiophate* if administered quickly enough.

3.Therapeutic uses: Historically, a topical ophthalmic solution of the *echothiophate* was used for the treatment of open-angle glaucoma. However, due to its side effect profile, which includes the risk of developing cataracts, *echothiophate* was rarely used and is no longer available. Figure 4.11 summarizes actions of some cholinergic agonists.

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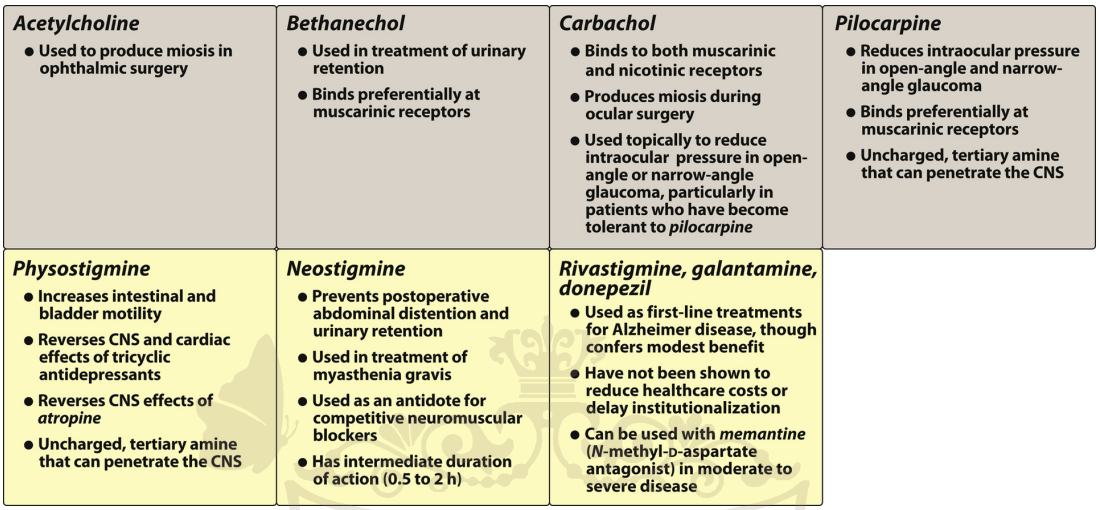

Figure 4.11 Summary of actions of some cholinergic agonists.CNS = central nervous system.

VII. TOXICOLOGY OF ANTICHOLINESTERASE AGENTS

Irreversible AChE inhibitors (mostly organophosphate compounds) are commonly used as agricultural insecticides in the United States, which has led to numerous cases of accidental poisoning with these agents. In addition, they are frequently used for suicidal and homicidal purposes. Organophosphate nerve gases such as *sarin* are used as agents of warfare and chemical terrorism. Toxicity with these agents is manifested as nicotinic and muscarinic signs and symptoms (cholinergic crisis). Depending on the agent, the effects can be just peripheral or can affect the whole body.

A. Reactivation of acetylcholinesterase

Pralidoxime [pral-i-DOX-eem] (2-PAM) can reactivate inhibited AChE (Figure 4.10). However, it is unable to penetrate into the CNS and therefore is not useful in treating the CNS effects of organophosphates. The presence of a charged group allows it to approach an anionic site on the enzyme, where it essentially

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displaces the phosphate group of the organophosphate and regenerates the enzyme. If given before aging of the alkylated enzyme occurs, it can reverse both muscarinic and nicotinic peripheral effects of organophosphates but not the CNS effects. With the newer nerve agents that produce aging of the enzyme complex within seconds, *pralidoxime* is less effective. In addition, it cannot overcome toxicity of reversible AChE inhibitors (for example, *physostigmine*).

B. Other treatments

Atropine is administered to prevent muscarinic side effects of these agents. Such effects include increased bronchial and salivary secretion, bronchoconstriction, and bradycardia. *Diazepam* is also administered to reduce the persistent convulsions caused by these agents. General supportive measures, such as maintenance of patent airway, oxygen supply, and artificial respiration, may be necessary as well.

Chapter Summary

- Cholinergic neurotransmission involves the synthesis of ACh, synaptic storage, release via Ca^{2+}-mediated exocytosis, binding to the receptor, degradation of ACh in the synaptic cleft by acetylcholinesterase (AChE), and recycling of choline.
- Cholinoceptors are classified as either muscarinic or nicotinic receptors.
- Nicotinic receptors are directly coupled to cation channels (ionotropic receptor) and mediate fast excitatory synaptic transmission at the neuromuscular junction (NMJ), the adrenal medulla, autonomic ganglia, and various sites in the CNS.
- Muscarinic receptors mediate acetylcholine effects at postganglionic parasympathetic synapses (mainly heart, smooth muscle, and glands) and contribute to ganglionic excitation. They occur in many parts of the CNS. All muscarinic receptors are activated by acetylcholine and blocked by *atropine.*
- Muscarinic receptors are G protein–coupled receptors (metabotropic receptors) and signal through either activation of phospholipase C (M_1, M_3) or inhibition of adenylyl cyclase, activation of potassium channels and/or inhibition of calcium channels.

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- Cholinergic agonists mimic the effects of ACh by binding directly to cholinoceptors (muscarinic or nicotinic) or indirectly by inhibiting acetylcholinesterase (AChE), which breaks down ACh.
- Muscarinic receptor agonists (for example, acetylcholine, *carbachol,* and *pilocarpine*) vary in their susceptibility to cholinesterase. Their main effects are bradycardia and vasodilation, contraction of visceral smooth muscle, exocrine secretions, pupillary constriction, and ciliary muscle contraction leading to a decrease of intraocular pressure. The adverse effects are usually an extension of these pharmacologic effects.
- The primary use of muscarinic agonists is in the treatment of glaucoma, urinary retention, and xerostomia.
- Anticholinesterase drugs may be reversible (*neostigmine*, *physostigmine*, *donepezil*, *rivastigmine*, *galantamine*) or irreversible (organophosphates). They differ in their chemical interaction with the active site of cholinesterase.
- Anticholinesterase drugs enhance cholinergic transmission at the autonomic synapses and the NMJ. Their main autonomic effects include bradycardia, hypotension, excessive secretions, bronchoconstriction, gastrointestinal hypermotility, and decrease of intraocular pressure. Their primary use is in the treatment of myasthenia gravis and Alzheimer disease.
- Anticholinesterase poisoning may occur from exposure to insecticides or nerve gases.

STUDY QUESTIONS

Choose the ONE best answer.

4.1 Which of the following drugs is correctly matched to its mechanism of action?

A. Bethanechol—nicotinic agonist
B. Pilocarpine—muscarinic antagonist
C. Pyridostigmine—inhibitor of AChE enzyme
D. Atropine—muscarinic agonist

Correct answer = C. Pyridostigmine is an inhibitor of acetylcholinesterase enzyme. Bethanechol (choline ester) lacks nicotinic actions (due to addition of the methyl group) but does have strong muscarinic activity. Pilocarpine (alkaloid)

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is also a muscarinic agonist, whereas atropine is an antagonist at muscarinic receptors.

4.2 A patient develops urinary retention after an abdominal surgery. Urinary obstruction was ruled out in this patient. Which of the following strategies would be helpful in promoting urination?

A. Activating nicotinic receptors
B. Inhibiting the release of acetylcholine
C. Inhibiting cholinesterase enzyme
D. Blocking muscarinic receptors

Correct answer = C. Activation of muscarinic receptors in the detrusor muscle of the urinary bladder can promote urination in patients where the tone of detrusor muscle is low. Inhibiting cholinesterase enzyme increases the levels of acetylcholine, and acetylcholine can increase the tone of the detrusor muscle. There are no nicotinic receptors in the detrusor muscle; therefore, activation of nicotinic receptors is not helpful. Inhibiting the release of acetylcholine or blocking muscarinic receptors worsens urinary retention.

4.3 If an ophthalmologist wants to dilate the pupils for an eye examination, which of the following drugs/class of drugs is theoretically useful?

A. Muscarinic receptor activator (agonist)
B. Muscarinic receptor inhibitor (antagonist)
C. Pilocarpine
D. Neostigmine

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Correct answer = B. Muscarinic agonists (for example, pilocarpine) contract the circular smooth muscles in the iris sphincter and constrict the pupil (miosis). Anticholinesterases (for example, neostigmine, physostigmine) also cause miosis by increasing the level of ACh. Muscarinic antagonists, on the other hand, relax the circular smooth muscles in the iris sphincter and cause dilation of the pupil (mydriasis).

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4.4 A 60-year-old woman who had a cancerous growth in the neck region underwent radiation therapy. Her salivary secretion was reduced due to radiation and she suffers from dry mouth (xerostomia). Which of the following drugs would be most useful in treating xerostomia in this patient?

A. Acetylcholine
B. Pilocarpine
C. Rivastigmine
D. Atropine

Correct answer = B. Salivary secretion may be enhanced by activating muscarinic receptors in the salivary glands. This can be achieved in theory by using a muscarinic agonist or an anticholinesterase agent. Pilocarpine is a muscarinic agonist administered orally for this purpose. Acetylcholine has similar effects as that of pilocarpine; however, it cannot be used therapeutically as it is rapidly destroyed by cholinesterase in the body. Rivastigmine is a cholinesterase inhibitor, but it is specifically used to delay the progression of Alzheimer disease. Atropine is a muscarinic antagonist and worsens dry mouth.

4.5 A 40-year-old man presents to his family physician with drooping eyelids, difficulty in chewing and swallowing, and muscle fatigue. He is diagnosed with myasthenia gravis. Which of the following agents is likely to be used in the treatment of this patient's condition?

A. Atropine
B. Neostigmine
C. Pralidoxime
D. Acetylcholine

POLE STAR

Correct answer = B. The function of nicotinic receptors in skeletal muscles is diminished in myasthenia gravis due to the development of antibodies to nicotinic receptors (autoimmune disease). Any drug that increases levels of ACh in the neuromuscular junction can improve symptoms in myasthenia gravis. Thus, neostigmine, a reversible cholinesterase inhibitor can be used to manage the symptoms of myasthenia gravis. Atropine is a muscarinic antagonist and has no role in skeletal muscle function. Pralidoxime is a drug that is used to reverse

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the binding of irreversible cholinesterase inhibitors with cholinesterase enzyme and helps to reactivate cholinesterase enzyme. Hence, pralidoxime will not be useful in improving skeletal muscle function in myasthenia gravis.

4.6 A 60-year-old woman with urinary retention is being treated with bethanechol. What side effect should she be cautioned about while taking this medication?

A. Xerostomia
B. Dry eyes
C. Constipation
D. Diaphoresis

Correct answer = D. Bethanechol is a muscarinic receptor agonist. The side effects this patient might experience are a predictable extension of pharmacological of muscarinic receptor stimulation. This includes diaphoresis, diarrhea, abdominal cramps, lacrimation, salivation, bradycardia, and bronchial secretion.

4.7 A 79-year-old man is diagnosed with Alzheimer disease. Which of the following drugs would be beneficial as a first line of treatment for this patient?

A. Carbachol
B. Physostigmine
C. Bethanechol
D. Donepezil

Correct answer = D. Donepezil is an anticholinesterase used as a first-line treatment for Alzheimer disease. It confers a modest benefit to patients by delaying the progression of the disease. However, it cannot stop the disease progression.

4.8 A 53-year-old woman suffering from open-angle glaucoma was prescribed pilocarpine to help control her intraocular pressure. The therapeutic effect of pilocarpine is most likely due to:

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A. Inhibition of carbonic anhydrase
B. Inhibition of acetylcholinesterase
C. Activation of muscarinic M_3 receptors
D. Blockade of β-adrenergic receptors

Correct answer = C. Pilocarpine is an alkaloid, which is stable to hydrolysis by acetylcholinesterase. Topical administration of pilocarpine activates muscarinic M_3 receptors. Activation of muscarinic M_3 receptors leads to contraction of the ciliary muscle, causing the trabecular meshwork and Schlemm canal to open. This increases the outflow of aqueous humor resulting in a decreased intraocular pressure.

4.9 A 57-year-old man is accidently poisoned with atropine. Which of the following can be used to reverse the CNS effects?

A. Carbachol
B. Acetylcholine
C. Neostigmine
D. Physostigmine

Correct answer = D. Physostigmine is a cholinesterase inhibitor, which easily crosses the blood–brain barrier because of its lipophilic nature. This makes physostigmine effective in reversing CNS effects of anticholinergic poisoning.

4.10A 9-year-old girl was brought unconscious to the emergency room within 1 hour after eating an apple contaminated with organophosphate insecticide. She presented with diarrhea, frequent urination, convulsions, breathing difficulties, pinpoint pupils, moist skin, and profuse salivation. Which of the following drug combinations would be the most appropriate for her condition?

A. Atropine and physostigmine
B. Atropine and pralidoxime
C. Physostigmine and pralidoxime
D. Physostigmine and pilocarpine

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Correct answer = B. The patient's signs and symptoms are consistent with that of cholinergic crisis, which occurs with an organophosphate poisoning. Atropine is administered to prevent muscarinic side effects of these agents. The organophosphate inhibition of AChE is initially reversible, but "ages" into an enzyme inhibition that is resistant to hydrolysis and reactivation. Since the patient was rushed to the emergency department within an hour of poisoning, pralidoxime, a cholinesterase reactivator, could still be effective in reversing both muscarinic and nicotinic peripheral effects of the organophosphate poison.

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5

Cholinergic Antagonists

Carinda Feild, Felix Amissah, Rosemary A. Poku

I. OVERVIEW

Cholinergic antagonist is a general term for agents that bind to cholinoceptors (muscarinic or nicotinic) and prevent the effects of acetylcholine (ACh) and other cholinergic agonists. The most clinically useful of these agents are selective blockers of muscarinic receptors. They are commonly known as anticholinergic agents (a misnomer, as they antagonize only muscarinic receptors), antimuscarinic agents (more accurate terminology), or parasympatholytics. The effects of parasympathetic innervation are thus, interrupted by these agents, and the actions of sympathetic innervation are left unopposed. A second group of drugs, the ganglionic blockers, shows a preference for nicotinic receptors at the sympathetic and parasympathetic ganglia. Clinically, they are the least important cholinergic antagonists. A third family of compounds, the neuromuscular blocking agents (mostly nicotinic antagonists), interfere with transmission of efferent impulses to skeletal muscles. These drugs are used as skeletal muscle relaxants in surgical anesthesia and as agents to facilitate intubation in surgical and critical care patients. Figure 5.1 summarizes the cholinergic antagonists discussed in this chapter.

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ANTIMUSCARINIC AGENTS

Aclidinium TUDORZA
Atropine GENERIC ONLY
Benztropine COGENTIN
Cyclopentolate CYCLOGYL
Darifenacin ENABLEX
Fesoterodine TOVIAZ
Glycopyrrolate GLYRX-PF, LONHALA
Hyoscyamine ANASPAZ, LEVSIN, SYMAX
Ipratropium ATROVENT
Oxybutynin DITROPAN, GELNIQUE, OXYTROL
Scopolamine TRANSDERM SCŌP
Solifenacin VESICARE
Tiotropium SPIRIVA
Tolterodine DETROL
Trihexyphenidyl GENERIC ONLY
Tropicamide MYDRIACYL
Trospium GENERIC ONLY
Umeclidinium INCRUSE ELLIPTA

GANGLIONIC BLOCKERS

Nicotine NICODERM, NICORETTE, NICOTROL

NEUROMUSCULAR BLOCKERS

Cisatracurium NIMBEX
Mivacurium MIVACRON
Pancuronium GENERIC ONLY
Rocuronium GENERIC ONLY
Succinylcholine ANECTINE, QUELICIN
Vecuronium GENERIC ONLY

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Figure 5.1 Summary of selected cholinergic antagonists.

II. ANTIMUSCARINIC AGENTS

Commonly known as anticholinergic drugs, these agents (for example, *atropine* and *scopolamine*) block muscarinic receptors (Figure 5.2), causing inhibition of muscarinic functions. In addition, these drugs block the effect of the few exceptional sympathetic neurons that are cholinergic, such as those innervating sweat glands, where muscarinic receptors are involved. Because they do not block nicotinic receptors, the anticholinergic drugs (more precisely, antimuscarinic drugs) have little or no action at skeletal neuromuscular junctions (NMJs) or autonomic ganglia. The anticholinergic drugs are beneficial in a variety of clinical situations as outlined below. [Note: A number of antihistamines and antidepressants (mainly tricyclic antidepressants) also have antimuscarinic activity.]

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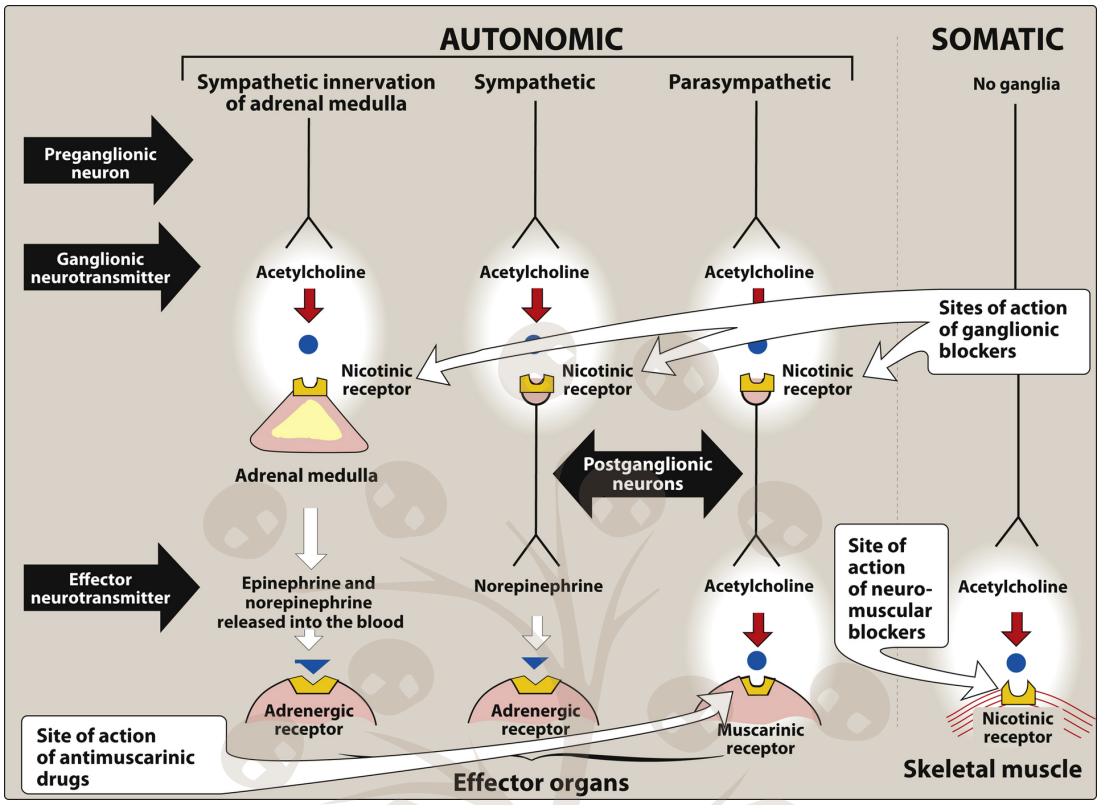

Figure 5.2 Sites of action of cholinergic antagonists.

A. Atropine

Atropine [A-troe-peen] is a tertiary amine extracted from belladonna alkaloid. It has a high affinity for muscarinic receptors and binds competitively to prevent ACh from binding (Figure 5.3). As a nonpolar tertiary amine, *atropine* is capable of crossing the blood–brain barrier and acting both centrally and peripherally. General actions last about 4 hours; however, effects of topical administration in the eye may persist for days. Effector organs have varying sensitivity to *atropine.* The greatest inhibitory effects are seen in bronchial tissue, salivary and sweat glands, and the heart.

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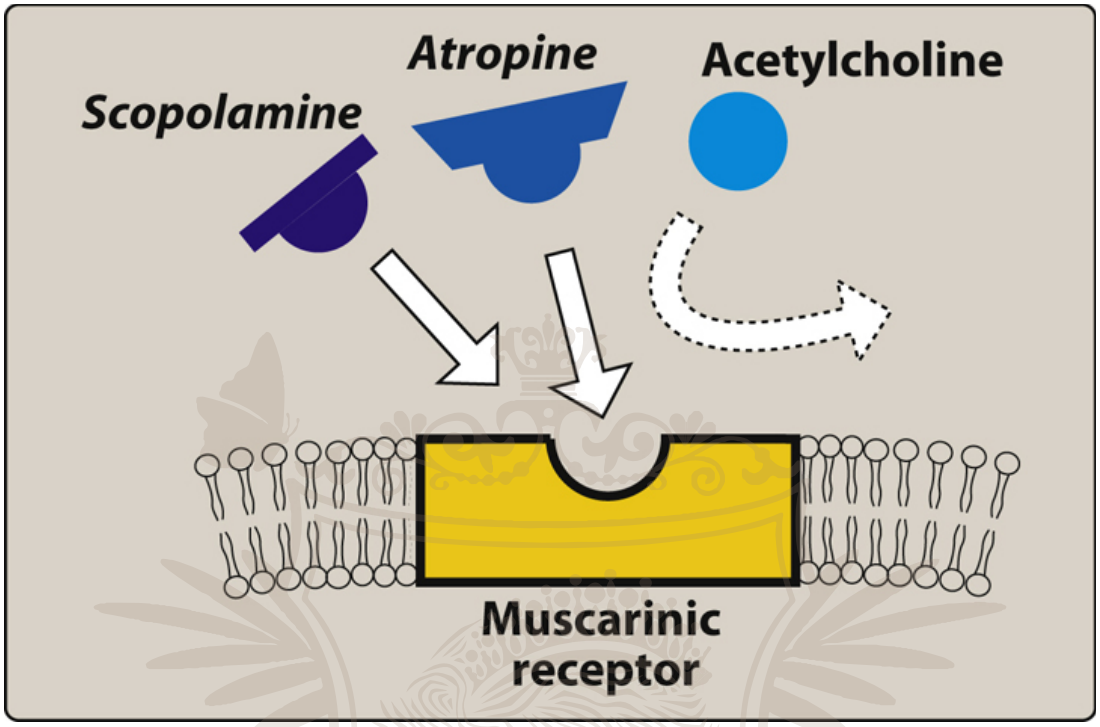

Figure 5.3 Competition of *atropine* and *scopolamine* with acetylcholine for the muscarinic receptor.

1. Actions

a. Eye: *Atropine* blocks muscarinic activity (M_3) in the eye, resulting in mydriasis (dilation of the pupil), unresponsiveness to light, and cycloplegia (inability to focus for near vision). In patients with angle-closure glaucoma, intraocular pressure may rise dangerously.

b. Gastrointestinal: *Atropine* (as the active isomer, *l*-*hyoscyamine* [hi-oh-SYE-uh-meen]) can be used as an antispasmodic to reduce activity of the GI tract. *Atropine* and *scopolamine* (discussed below) are probably the most potent antispasmodic drugs available. Although gastric motility is reduced, hydrochloric acid production is not significantly affected. Thus, *atropine* is not effective for the treatment of ulcers. Doses of *atropine* that reduce spasms

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also reduce saliva secretion, ocular accommodation, and urination. These effects decrease compliance with *atropine*.

c. Exocrine glands: *Atropine* blocks muscarinic receptors (mostly M_3) in the salivary glands, thereby reducing the production of saliva (antisialagogue) and producing dryness of the mouth (xerostomia). The salivary glands are exquisitely sensitive to *atropine.* Sweat and lacrimal glands are similarly affected. [Note: Inhibition of secretions of sweat glands can cause elevated body temperature, which can be dangerous in children and the elderly.]

d. Cardiovascular: *Atropine* produces divergent effects on the cardiovascular system, depending on the dose (Figure 5.4). At low doses, the predominant effect is a slight decrease in heart rate. This effect results from blockade of M_1 receptors on the inhibitory prejunctional (or presynaptic) neurons, thus permitting increased ACh release. Higher doses of *atropine* cause a progressive increase in heart rate by blocking M_2 receptors on the sinoatrial node.

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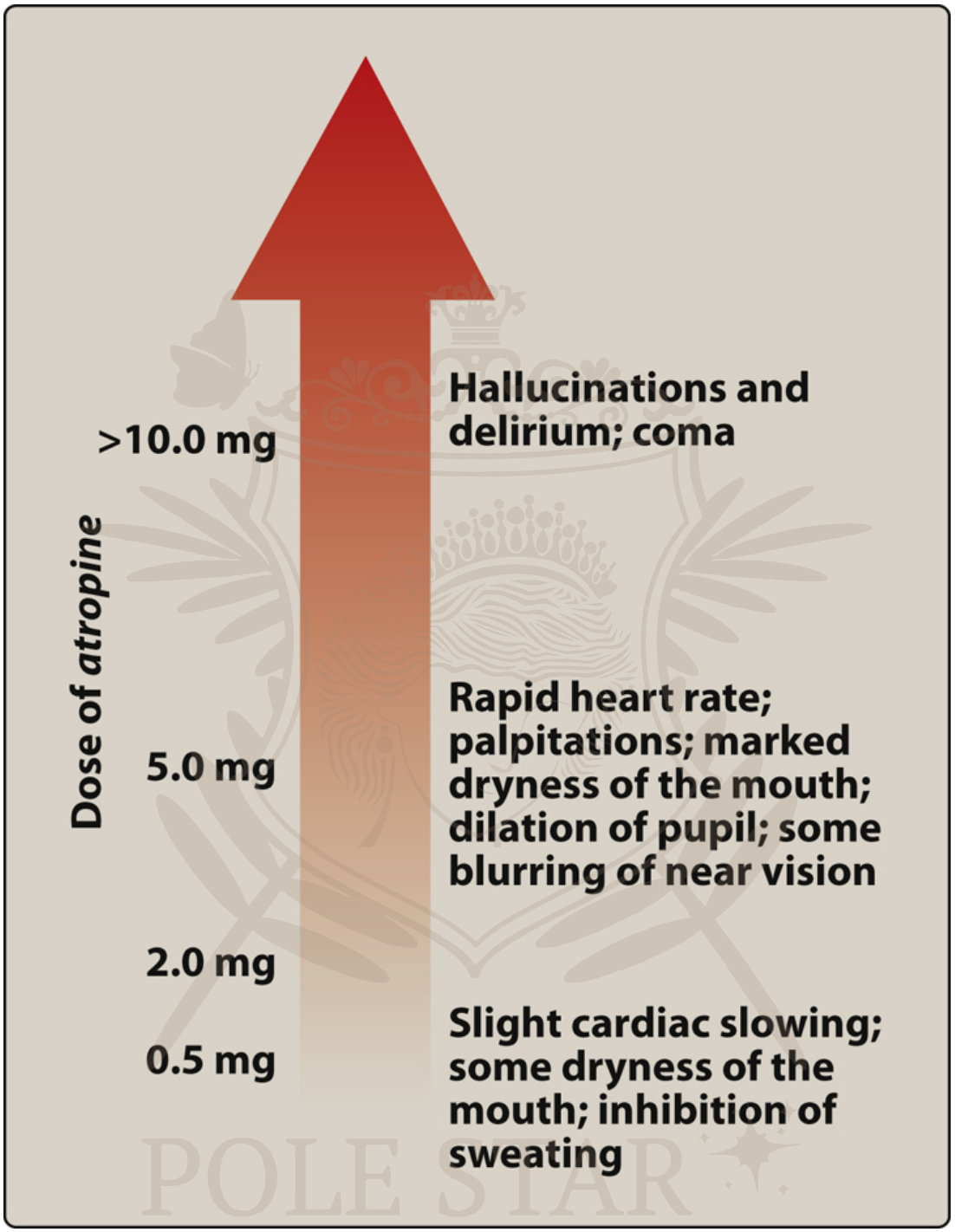

Figure 5.4 Dose-dependent effects of *atropine*.

e. Pulmonary: *Atropine* causes bronchodilation. Because of side effects associated with systemic absorption, other antimuscarinic agents (see below) are

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used clinically for this purpose. In addition, muscarinic blockade can decrease respiratory secretions.

2. Therapeutic uses

a. Ophthalmic: Topical *atropine* exerts both mydriatic and cycloplegic effects, and it permits the measurement of refractive errors without interference by the accommodative capacity of the eye. Thus, it has found use in ophthalmic examinations and procedures. Shorter-acting antimuscarinics (*cyclopentolate* [sye-kloe-PEN-toe-late] and *tropicamide* [troe-PIK-a-mide]) have largely replaced *atropine* due to prolonged mydriasis observed with *atropine* (7-14 days vs. 6-24 hours with other agents). [Note: *Phenylephrine* or similar α-adrenergic agonists are preferred for pupillary dilation if cycloplegia is not required.]

b. Antispasmodic: *Atropine, hyoscyamine,* and *scopolamine* are used as antispasmodic agents to relax the GI tract.

c. Cardiovascular: Injectable *atropine* is used to increase heart rate in the treatment of symptomatic bradycardia.

d. Antidote for cholinergic agonists: *Atropine* is used for the treatment of organophosphate (insecticides, nerve gases) poisoning (see Chapters 4 and 46), to counteract the muscarinic effect of other clinically used anticholinesterases (agents that decrease the breakdown of acetylcholine, such as *physostigmine)*, and in some types of mushroom poisoning (certain mushrooms contain muscarine, an alkaloid that mimics the effect of ACh at the muscarinic receptor). Continued dosing of injectable *atropine* may be required over a long period to counteract the poisons. The ability of *atropine* to enter the central nervous system (CNS) is of particular importance in treating central toxic effects of anticholinesterases.

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3.Pharmacokinetics: *Atropine* is readily absorbed, partially metabolized by the liver, and eliminated primarily in urine. It has a half-life of about 4 hours.

4.Adverse effects: Depending on the dose, *atropine* may cause dry mouth, blurred vision, “sandy eyes,” tachycardia, urinary retention, and constipation. Effects on the CNS include restlessness, confusion, hallucinations, and delirium, which may progress to depression, collapse of the circulatory and respiratory systems, and death. Because of the ability of *atropine* to cross the blood–brain barrier and act centrally, geriatric patients are at substantial risk of confusion, disorientation, and depressed cognitive function. The drug may be dangerous in children, because they are sensitive to its effects, particularly to rapid increases in body temperature. Low doses of cholinesterase inhibitors, such as *physostigmine*, may be used to overcome *atropine* toxicity. *Atropine* may also induce troublesome urinary retention.

B. Scopolamine

Scopolamine [skoe-POL-a-meen], another tertiary amine plant alkaloid, produces peripheral effects similar to those of *atropine.* However, *scopolamine* has greater action on the CNS (unlike *atropine*, CNS effects are observed at therapeutic doses) and a longer duration of action as compared with *atropine.* It has some special actions as indicated below.

1.Actions: *Scopolamine* is one of the most effective drugs available for motion sickness (Figure 5.5). It also has the unusual effect of blocking short-term memory. In contrast to *atropine*, *scopolamine* produces sedation, but at higher doses, it can produce excitement. *Scopolamine* may produce euphoria and is susceptible to abuse.

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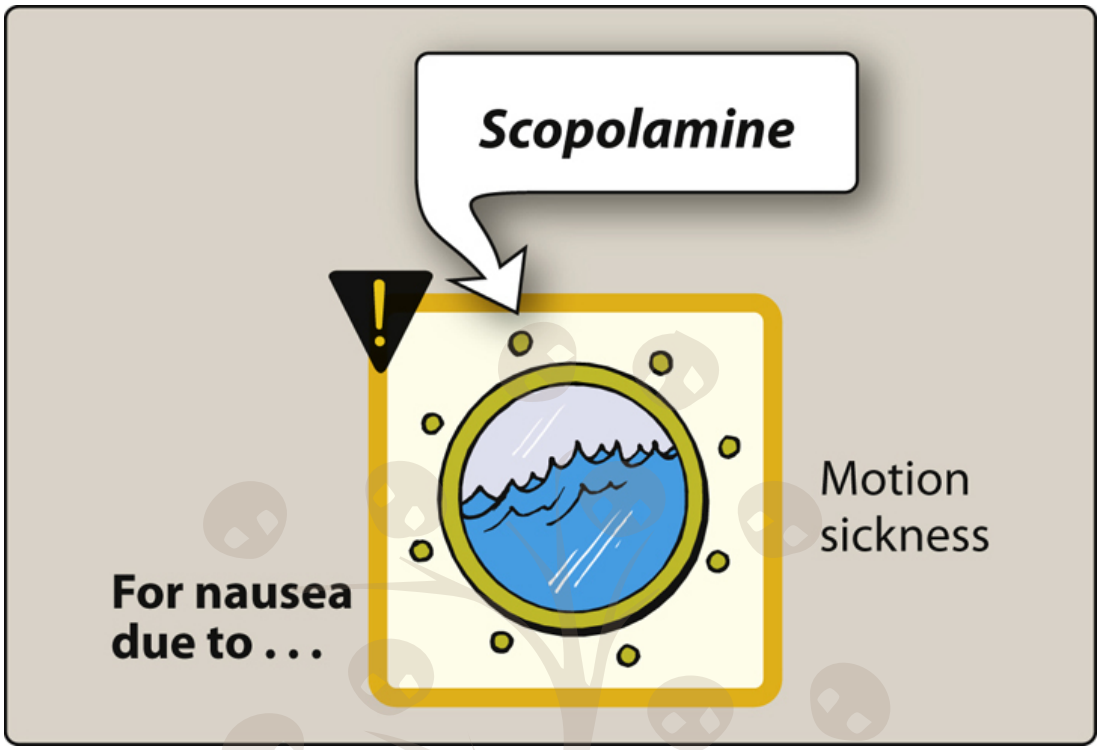

Figure 5.5 *Scopolamine* is an effective agent for motion sickness.

2. Therapeutic uses: The most common therapeutic indications for *scopolamine* include prevention of motion sickness and postoperative nausea and vomiting (PONV). For both PONV and motion sickness, it is available as a topical patch that provides effects for up to 3 days. [Note: As with all drugs used for motion sickness, it is much more effective prophylactically than for treating motion sickness or PONV once it occurs.]

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Clinical Application 5.1: Scopolamine Use in Emesis

Scopolamine blocks muscarinic receptors in the vestibular system and stops signaling to the CNS. It is used to prevent and treat **motion sickness** as well as prevent **PONV.** *Scopolamine* is available as an adhesive **transdermal patch** that is effective for up to 72 hours after application. This may be beneficial for patients unable to tolerate oral medications or those requiring continuous prevention of motion sickness (for example, passengers on cruise ships). Transdermal *scopolamine* should be applied 4 hours before anticipated motion

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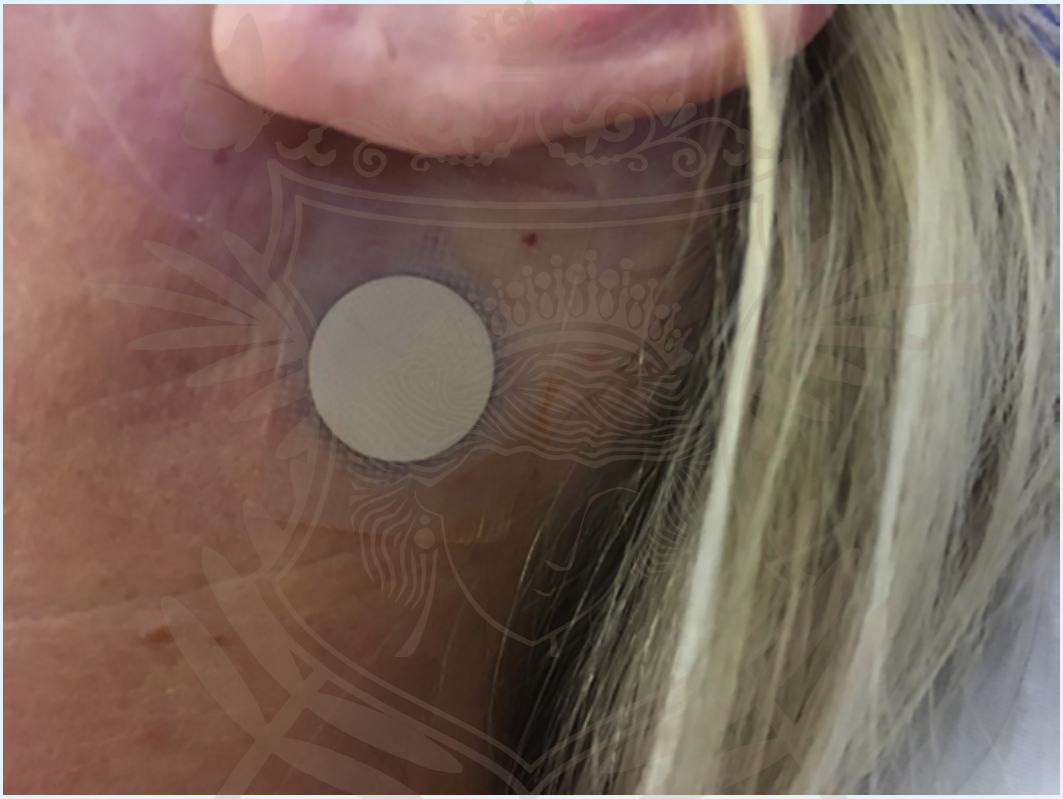
sickness triggers and the evening before surgery if used to prevent PONV. The patch should be applied to the skin behind one ear. *Scopolamine* is associated with adverse effects such as sedation, visual disturbances, dry mouth, and dizziness. These adverse effects are worsened when a patient is concurrently taking a cholinergic antagonist. Also, this agent should be used with caution in older adults because of depressed or altered cognition.



Scopolamine patch should be applied behind one ear.From E. S.Guimaraes , M.Davis , J. R.Kirsch , and G.Woodworth . *The Anesthesia Technologist's Manual*, 2nd ed. Wolters Kluwer, (2019), Figure 19.7.

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3.Pharmacokinetics and adverse effects: These aspects are similar to those of *atropine*, with the exception of longer half-life.

C. Ipratropium and other antimuscarinic respiratory agents

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Ipratropium [i-pra-TROE-pee-um] is a quaternary derivative of *atropine*, and *tiotropium* [TYE-oh-TROE-pee-um], *glycopyrrolate* [glye-koe-PYE-roe-late], *aclidinium* [a-kli-DIN-ee-um], and *umeclidinium* [ue-ME-kli-DIN-ee-um] are synthetic quaternary compounds. These agents produce bronchodilation via antagonism of the M_3 receptor in the airway smooth muscle. *Ipratropium* is classified as a short-acting muscarinic antagonist (SAMA), while the other agents are classified as long-acting muscarinic antagonists (LAMAs) based on the duration of action. These agents are approved as bronchodilators for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). *Ipratropium* and *tiotropium* are also used in the acute management of bronchospasm in asthma and chronic management of asthma, respectively (see Chapter 41). All of these agents are delivered via inhalation. Because of the positive charge, these drugs do not enter the systemic circulation or the CNS, restricting effects to the pulmonary system. [Note: *Glycopyrrolate* is also available as an injectable form, and it is administered before surgery to reduce salivary and respiratory secretions and prevent accumulation of mucus in the airways.]

Clinical Application 5.2 Antimuscarinic Therapy in Asthma and COPD

Antimuscarinics are effective bronchodilators in asthma and COPD. They attenuate but do not block allergen-induced asthma and exercise-induced bronchoconstriction. In COPD, antimuscarinic agents inhibit the vagal input in smooth muscle tone and can serve as the mainstay of bronchodilator therapy. *Ipratropium* is a nonselective muscarinic antagonist that is used as an adjunct therapy in acute asthma exacerbation that does not respond to β_2-agonists alone. *Tiotropium* is a long-acting inhaled anticholinergic. It has a higher affinity for muscarinic receptors than *ipratropium. Tiotropium* may be considered as add-on therapy in asthma patients 6 years and older whose asthma is not controlled with inhaled corticosteroids and a long-acting β agonist. The addition of *tiotropium* improves lung function and increases the time to severe exacerbation requiring oral corticosteroid therapy.

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D. Tropicamide and cyclopentolate

These agents are used as ophthalmic solutions for mydriasis and cycloplegia. Their duration of action is shorter than that of *atropine. Tropicamide* produces mydriasis for 6 hours and *cyclopentolate* for 24 hours.

E. Benztropine and trihexyphenidyl

Benztropine and *trihexyphenidyl* are useful as adjuncts in the treatment of Parkinson disease (see Chapter 15) and other types of parkinsonian syndromes, including antipsychotic-induced extrapyramidal symptoms.

F. Oxybutynin and other antimuscarinic agents for overactive bladder

Oxybutynin [ox-i-BYOO-ti-nin], *darifenacin* [dar-e-FEN-a-sin], *fesoterodine* [fes-oh-TER-oh-deen], *solifenacin* [sol-ee-FEN-a-sin], *tolterodine* [tol-TER-oh-deen], and *trospium* [TROSE-pee-um] are synthetic antimuscarinic drugs.

1. Actions: These agents competitively block muscarinic (M_3) receptors in the bladder. This results in reduced intravesical pressure, increased bladder capacity, and reduced frequency of bladder contractions. Antimuscarinic actions at M_3 receptors in the GI tract, salivary glands, CNS, and eye may cause adverse effects. *Darifenacin* and *solifenacin* are relatively more selective M_3 muscarinic receptor antagonists. However, the other drugs are mainly nonselective muscarinic antagonists, and binding to other muscarinic receptor subtypes may contribute to adverse effects.

2. Therapeutic uses: These agents are used for management of overactive bladder and urinary incontinence. *Oxybutynin* is also used in patients with neurogenic bladder.

3. Pharmacokinetics: All of the agents are available in oral dosage forms. Most agents have a long half-life, which allows

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once-daily administration. [Note: Immediate-release *oxybutynin* and *tolterodine* must be dosed two or more times daily; however, extended-release formulations of these agents allow for once-daily dosing.] *Oxybutynin* is also available in a transdermal patch and topical gel formulation. These drugs are hepatically metabolized by the cytochrome P450 system (primarily CYP 3A4 and 2D6), with the exception of *trospium*, which is thought to undergo ester hydrolysis.

4.Adverse effects: Side effects include dry mouth, constipation, and blurred vision, which limit tolerability of these agents. Extended-release formulations and the transdermal patch have a lower incidence of adverse effects and may be better tolerated. *Trospium* is a quaternary compound that minimally crosses the blood–brain barrier and has fewer CNS effects than do other agents, making it a preferred choice in treating overactive bladder in geriatric patients, particularly those at risk for cognitive dysfunction. Important characteristics of the muscarinic antagonists are summarized in Figures 5.6 and 5.7.

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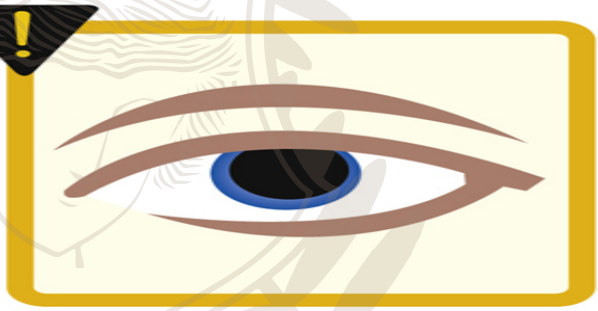
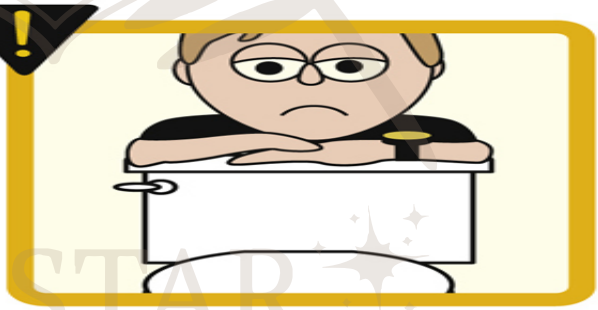
Blurred vision

Confusion

Mydriasis



Constipation



Urinary retention

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Figure 5.6 Adverse effects commonly observed with muscarinic antagonists.

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Drug	Therapeutic uses
Muscarinic blockers	
Trihexyphenidyl *Benztropine*	● Treatment of Parkinson disease ● Management of antipsychotic-induced extrapyramidal effects
Darifenacin *Fesoterodine* *Oxybutynin* *Solifenacin* *Tolterodine* *Trospium*	● Treatment of overactive urinary bladder
Cyclopentolate *Tropicamide* *Atropine**	● In ophthalmology, to produce mydriasis and cycloplegia prior to refraction
*Atropine**	● To treat spastic disorders of the GI tract ● To treat organophosphate poisoning ● To suppress respiratory secretions prior to surgery ● To treat bradycardia
Scopolamine	● To prevent motion sickness
Aclidinium *Glycopyrrolate* *Ipratropium* *Tiotropium* *Umeclidinium*	● Treatment of COPD
Ganglionic blockers	
Nicotine	● Smoking cessation

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Figure 5.7 Summary of cholinergic antagonists.*Contraindicated in angle-closure glaucoma. COPD = chronic obstructive pulmonary disease; GI = gastrointestinal.

Clinical Application 5.3: Anticholinergic Use in Urinary Incontinence

Antimuscarinic agents, which act at the M_3 receptor, are the first-line pharmacologic treatment to improve symptoms and quality of life in patients with urinary incontinence. They suppress impulsive detrusor contractions and enhance bladder storage. Antimuscarinic agents should be initiated with the lowest dose and gradually titrated upward based on clinical response and tolerability. The older immediate-release agent, *oxybutynin,* has been associated with higher rates of adverse events, decreasing patient compliance and reducing clinical response compared with newer agents and extended-release products (*oxybutynin XL, tolterodine LA, trospium ER, darifenacin ER*). Extended-release agents cause less dry mouth, and *trospium* is associated with fewer CNS side effects. *Oxybutynin* transdermal patch and topical gel are alternatives for patients who cannot take or tolerate oral dosage forms.

III. GANGLIONIC BLOCKERS

Ganglionic blockers act specifically on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia. Some also block the ion channels of the autonomic ganglia. These drugs show no selectivity toward the parasympathetic or sympathetic ganglia and are not effective as neuromuscular antagonists. Thus, these drugs block the entire output of the autonomic nervous system at the nicotinic receptor. With the exception of *nicotine* [NIK-oh-teen], ganglionic blockers are rarely used therapeutically, but often serve as tools in experimental pharmacology [for example, *mecamylamine*]. *Nicotine* is commonly known as a component of tobacco products, and pharmaceutical preparations of *nicotine* (for example, gum, patches, and lozenges) may be used to aid in

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smoking cessation. In higher doses, *nicotine* is a poison with many undesirable actions. Depending on the dose, *nicotine* depolarizes autonomic ganglia, resulting first in stimulation and then in paralysis of all ganglia. The stimulatory effects are complex and result from increased release of neurotransmitters (Figure 5.8), due to effects on both sympathetic and parasympathetic ganglia (see Chapter 22 for a full discussion of *nicotine*). [Note: Patients using *nicotine* products for smoking cessation should be cautioned to keep products out of reach of small children and pets due to the risk of toxic effects if excess quantities are consumed.]

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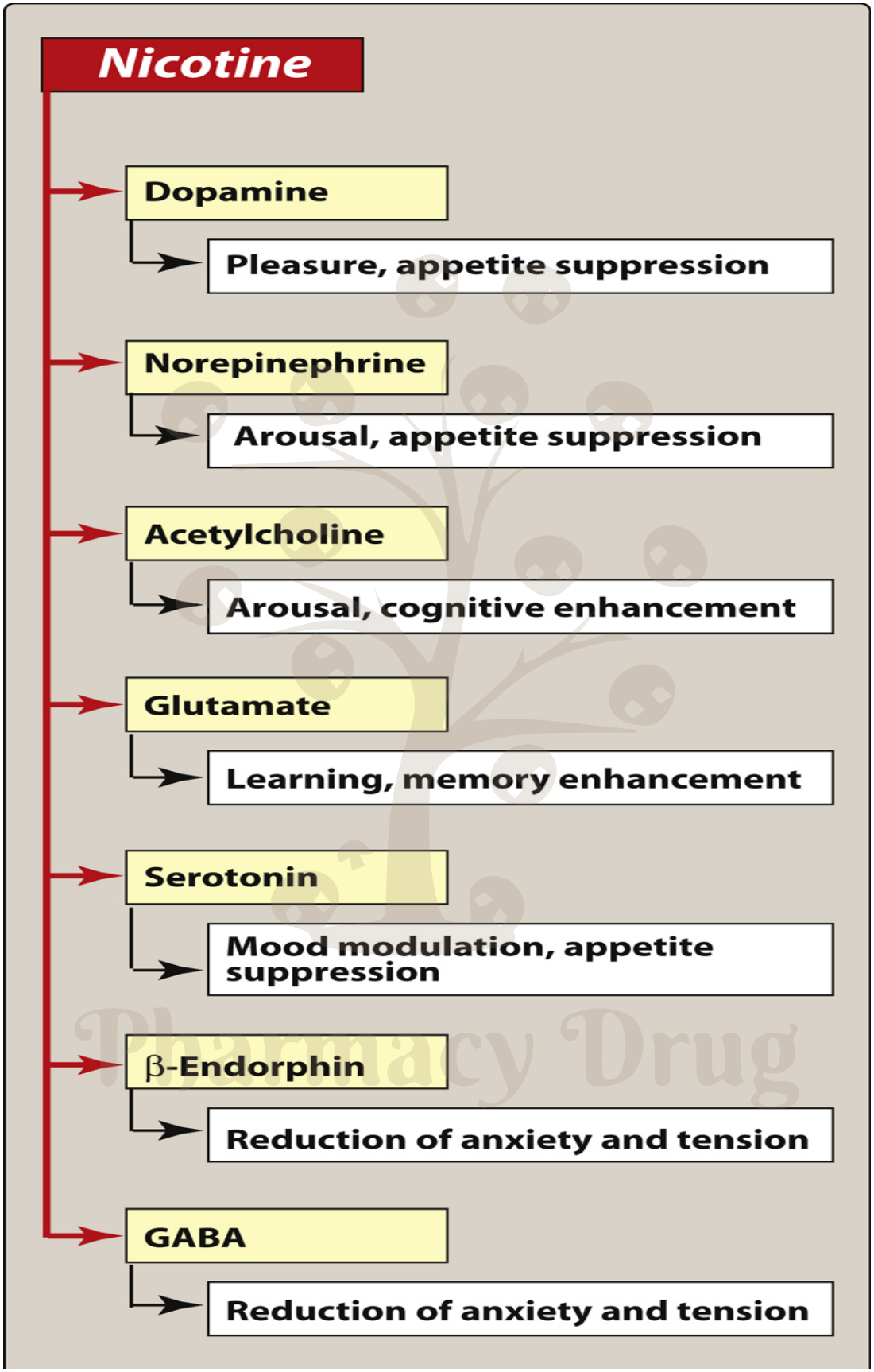

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Figure 5.8 Neurochemical effects of *nicotine*.GABA = γ-aminobutyric acid.

IV. NEUROMUSCULAR BLOCKING AGENTS

These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on skeletal muscle (see Figure 5.2). They possess some chemical similarities to ACh and act either as antagonists (nondepolarizing) or as agonists (depolarizing) at the receptors on the endplate of the NMJ. Neuromuscular blockers (NMBs) are clinically useful to facilitate endotracheal intubation and subsequent mechanical ventilation, as well as muscular relaxation in surgical procedures requiring a receptive operative field.

A. Nondepolarizing (competitive) blockers

The first known NMB was *curare* [kyoo-RAH-ree], which Amazon hunters used to paralyze prey by administering with a tinctured spear or dart. The development of *tubocurarine* [too-boe-kyoo-AR-een] followed, but it has been replaced by agents with fewer adverse effects, such as *cisatracurium* [cis-a-trah-CURE-ih-um], *mivacurium* [mi-vah-KYOO-ree-um], *pancuronium* [pan-kure-OH-nee-um], *rocuronium* [roe-kyoor-OH-nee-um], and *vecuronium* [ve-KYOO-roe-nee-um].

1. Mechanism of action: NMBs competitively block ACh at the nicotinic receptors (Figure 5.9) on skeletal muscle. They compete with ACh at the receptor without stimulating it, thus preventing depolarization of the muscle cell membrane and inhibiting subsequent muscular contraction.

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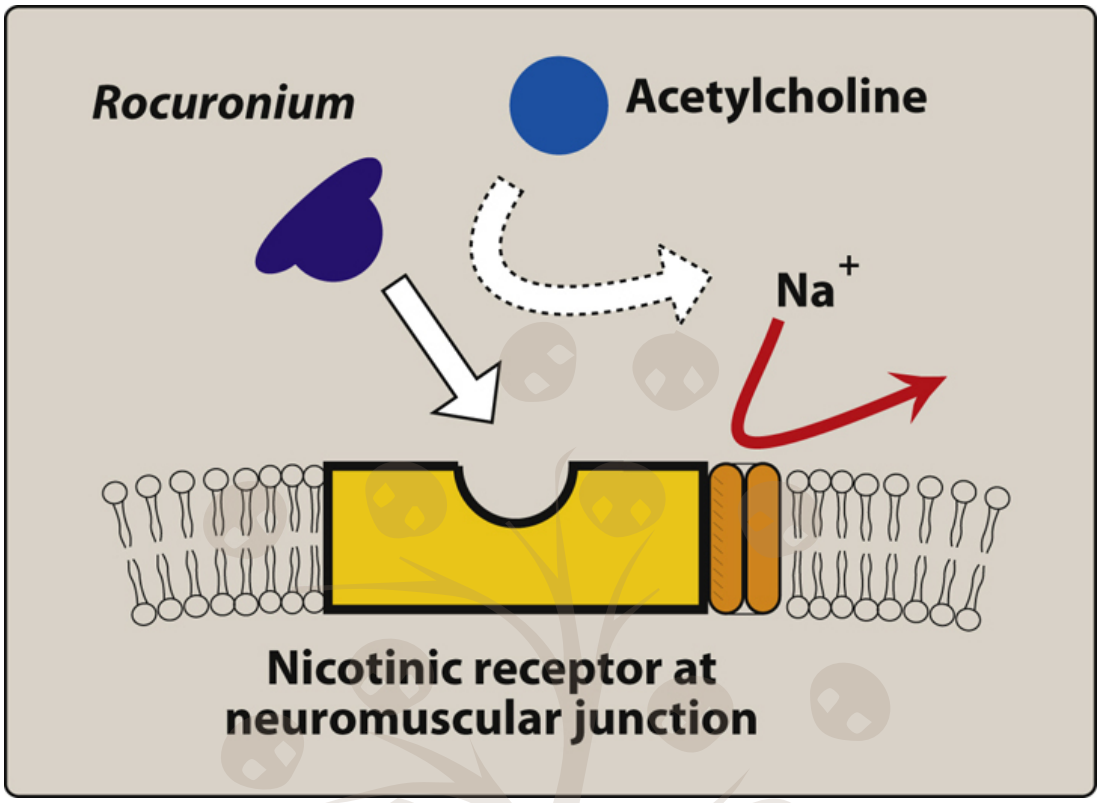

Figure 5.9 Mechanism of action of competitive neuromuscular blocking drugs.

2.Actions: Muscles have differing sensitivity to blockade by competitive NMB agents. Small, rapidly contracting muscles of the face and eye are most susceptible and are paralyzed first, followed by the fingers, limbs, neck, and trunk muscles. Next, the intercostal muscles are affected and, lastly, the diaphragm. The muscles recover in the reverse manner. The adequate dosing of nondepolarizing NMBs is weight-based and time-based and can be further evaluated and titrated by monitoring peripheral muscle strength with a peripheral nerve stimulator.

Following surgical procedures, reversal of the action of NMBs is needed to facilitate the recovery process. The competitive action of the NMBs at the nicotinic receptor can be counteracted by administration of cholinesterase inhibitors (for example *neostigmine*), which increases the available

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concentration of ACh in the NMJ. Clinicians employ this strategy to shorten the duration of neuromuscular blockade. When *neostigmine* is used to reverse neuromuscular blockade, it requires coadministration of an antimuscarinic drug (*glycopyrrolate*) to prevent bradycardia, salivation, and nausea and vomiting that can occur with use of this agent. Reversal of some nondepolarizing NMBs can also be accomplished with use of *sugammadex* [soo-GAM-ma-dex]. *Sugammadex* is a selective relaxant-binding agent that terminates the action of both *rocuronium* and *vecuronium* and can be used to speed recovery (see Chapter 20).

3. Pharmacokinetics: All NMBs are injected intravenously or occasionally intramuscularly. These agents possess two or more quaternary amines in their bulky ring structure that prevent absorption from the gut. They penetrate membranes very poorly and do not enter cells or cross the blood–brain barrier. Drug action is terminated in a variety of ways (Figure 5.10). *Pancuronium* is excreted unchanged in urine. *Cisatracurium* undergoes organ-independent metabolism (via Hofmann elimination) to laudanosine, which is further metabolized and renally excreted. The amino steroid drugs *vecuronium* and *rocuronium* are primarily deacetylated in the liver and excreted unchanged in bile. They are also renally excreted, although to a lesser degree than *pancuronium. Mivacurium* is eliminated by plasma cholinesterase. The choice of agent depends on the desired time of onset, duration of muscle relaxation, and the route of elimination. Characteristics of the neuromuscular-blocking drugs are shown in Figure 5.11.

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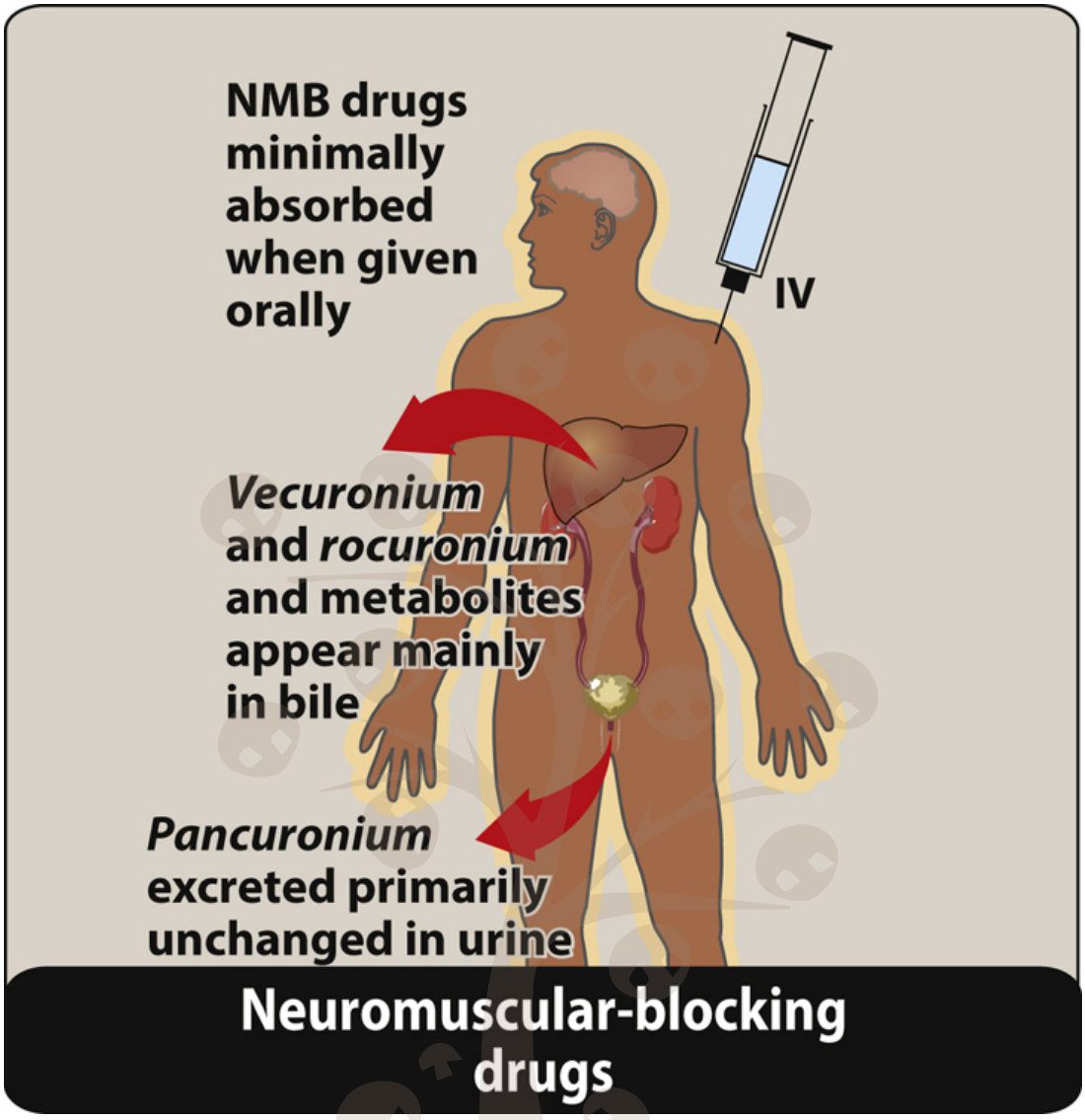

Figure 5.10 Pharmacokinetics of the neuromuscular blocking drugs.*Cisatracurium* undergoes organ-independent elimination. *Mivacurium* and *succinylcholine* are metabolized by plasma cholinesterase. IV = intravenous.

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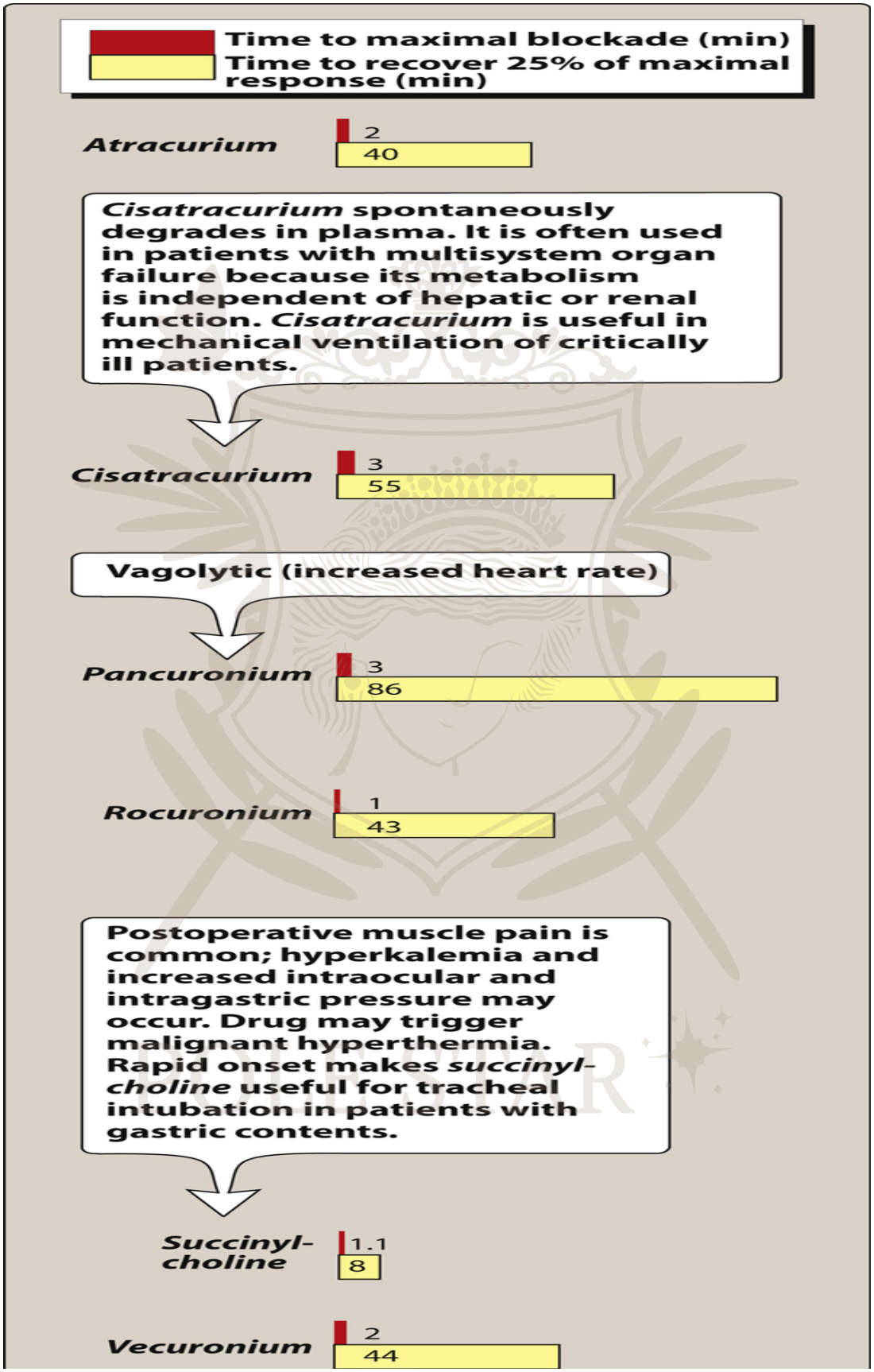
Time to maximal blockade (min)
Time to recover 25% of maximal response (min)
Atracurium
2
40
Cisatracurium spontaneously degrades in plasma. It is often used in patients with multisystem organ failure because its metabolism is independent of hepatic or renal function. Cisatracurium is useful in mechanical ventilation of critically ill patients.
Cisatracurium
3
55
Vagolytic (increased heart rate)
Pancuronium
3
86
Rocuronium
1
43
Postoperative muscle pain is common; hyperkalemia and increased intraocular and intragastric pressure may occur. Drug may trigger malignant hyperthermia. Rapid onset makes succinylcholine useful for tracheal intubation in patients with gastric contents.
Succinyl-choline
1.1
8
Vecuronium
2
44

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Figure 5.11 Characteristics of neuromuscular blocking drugs.

4. **Adverse effects:** In general, these agents are safe with minimal side effects. The adverse effects of the specific NMBs are shown in Figure 5.11.

5. **Drug interactions**

   a. **Cholinesterase inhibitors:** Drugs such as *neostigmine* and *physostigmine* can overcome the action of nondepolarizing NMBs. However, with increased dosage, cholinesterase inhibitors can cause a depolarizing block due to elevated ACh concentrations at the end plate membrane. If the NMB has entered the ion channel (is bound to the receptor), cholinesterase inhibitors are not as effective in overcoming blockade.

   b. **Halogenated hydrocarbon anesthetics:** Drugs such as *isoflurane*, *sevoflurane*, and *desflurane* act to enhance neuromuscular blockade by exerting a stabilizing action at the NMJ. These agents sensitize the NMJ to the effects of NMBs.

   c. **Aminoglycoside antibiotics:** Drugs such as *gentamicin* and *tobramycin* inhibit ACh release from cholinergic nerves by competing with calcium ions. They synergize with competitive blockers, enhancing neuromuscular blockade.

   d. **Calcium channel blockers:** These agents may increase the neuromuscular blockade of competitive blockers.

B. Depolarizing agents

Depolarizing neuromuscular blocking agents act by depolarizing the plasma membrane of the muscle fiber at the NMJ, similar to

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the action of ACh. However, these agents are more resistant to degradation by acetylcholinesterase (AChE) and can more persistently depolarize the muscle fibers. *Succinylcholine* [suk-sin-il-KOE-leen] is the only depolarizing muscle relaxant in use today.

1.Mechanism of action: *Succinylcholine* binds to the nicotinic receptor and acts like ACh to depolarize the NMJ (Figure 5.12). Unlike ACh, which is quickly metabolized by AChE, the depolarizing agent persists at high concentrations in the synaptic cleft, binding to the receptor for a longer time and providing sustained depolarization of the muscle cell. [Note: The duration of action is dependent on diffusion from the motor end plate and hydrolysis by plasma cholinesterase (also called butyrylcholinesterase or pseudocholinesterase). Genetic variants in which plasma cholinesterase levels are low or absent lead to prolonged neuromuscular paralysis.] The depolarizing agent first causes opening of the sodium channel associated with nicotinic receptors, which results in depolarization of the receptor (phase I). This leads to a transient twitching of the muscle (fasciculations). Continued binding of the depolarizing agent renders the receptor incapable of transmitting further impulses. With time, continuous depolarization gives way to gradual repolarization as the sodium channel closes or is blocked. This causes a resistance to depolarization (phase II) and flaccid paralysis.

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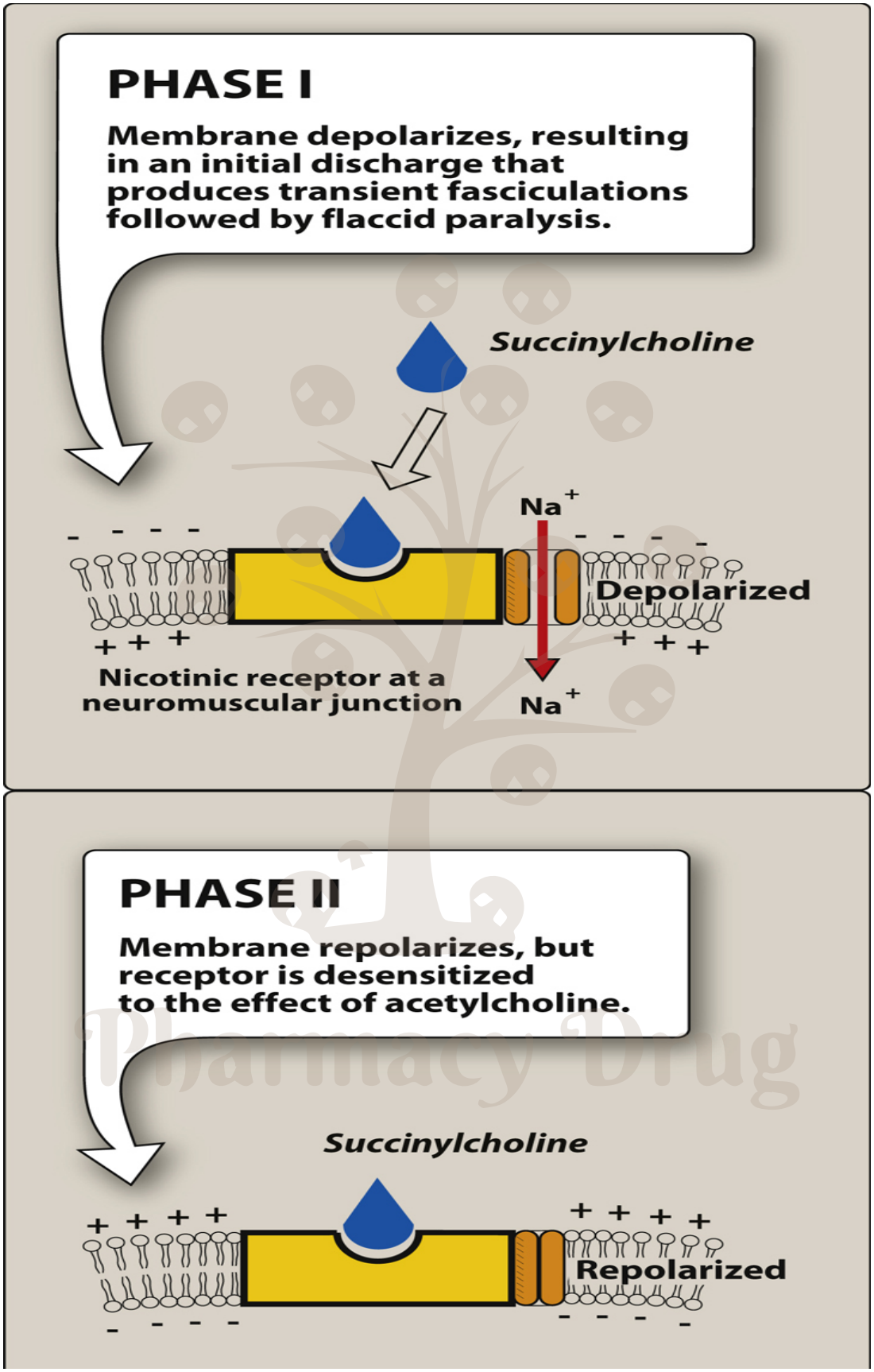

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Figure 5.12 Mechanism of action of depolarizing neuromuscular blocking drugs.

2.Actions: As with the nondepolarizing NMBs, the respiratory muscles (intercostals and diaphragm) have greater resistance to *succinylcholine* and are the last to relax and first to recover. *Succinylcholine* initially produces brief muscle fasciculations, which are readily visible and cause severe muscular soreness in up to 30% of patients. Normally, the duration of action of *succinylcholine* is short (5-8 minutes), due to rapid hydrolysis by plasma cholinesterase. However, *succinylcholine* that reaches the NMJ is not metabolized, allowing the agent to bind to nicotinic receptors, and its redistribution to plasma is necessary for metabolism.

3.Therapeutic uses: Because of its rapid onset of action, *succinylcholine* is useful when rapid endotracheal intubation is required or when the procedure requiring muscular relaxation is very brief (for example, electroconvulsive shock treatment).

4.Pharmacokinetics: *Succinylcholine* is injected intravenously or intramuscularly. Its brief duration of action results from redistribution and rapid hydrolysis by plasma cholinesterase. Drug effects rapidly disappear upon discontinuation.

5.Adverse effects

a. Hyperthermia: S*uccinylcholine* can potentially induce malignant hyperthermia in susceptible patients (see Chapter 20).

b. Prolonged muscular weakness: Administration of *succinylcholine* to a patient who is deficient in the quantity or quality (atypical form of the enzyme) of plasma

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cholinesterase can lead to a prolonged paralysis due to continued NMB activity.

c. Hyperkalemia: *Succinylcholine* causes depolarization at the NMJ, which results in efflux of intracellular potassium from the muscle into the plasma and a transient increase in potassium level. Under normal conditions, the body can handle the transient hyperkalemia. However, paralyzed or immobile patients, burn patients, trauma patients, and those with myopathies may have significant proliferation and upregulation of the nicotinic receptors, resulting in increased sensitivity to *succinylcholine.* In these patients, administration of *succinylcholine* can result in severe hyperkalemia that may cause cardiac arrhythmias or cardiac arrest. Use of *succinylcholine* should be avoided in these patients and those with preexisting hyperkalemia.

Clinical Application 5.4: Paralysis with Neuromuscular Blockers

When the nicotinic receptors on skeletal muscle are blocked, the result is paralysis. The depolarizing agent *succinylcholine* binds to the receptor, causes depolarization, and then remains on the receptor, thereby preventing repolarization and thus causing paralysis. This agent has a quick onset and short duration of action and is ideal for intubation for respiratory failure or intubation for surgical procedures in patients at risk of aspiration. Conversely, the nondepolarizing agents bind to the receptor but do not cause depolarization, and also cause paralysis. The nondepolarizing agents all have a longer onset and duration of action. These agents can be used in the intensive care unit or operating room to facilitate intubation and maintain paralysis. It is important to note that these medications affect skeletal muscle but not smooth muscle, and they provide no analgesia or sedation. Patients receiving these agents need scheduled sedation and pain medication implemented prior to initiation of NMB therapy.

Chapter Summary

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- Acetylcholine is the neurotransmitter for nicotinic receptors of the autonomic (sympathetic and parasympathetic) and somatic nervous system, as well as the muscarinic receptors of the parasympathetic nervous system.
- Cholinergic antagonists (anticholinergic agents) include drugs that block either muscarinic or nicotinic receptors and prevent the effects of acetylcholine and other cholinergic agonists.
- Agents that antagonize the muscarinic receptors are more specifically known as antimuscarinic agents. *Atropine* is the iconic muscarinic antagonist.
- Muscarinic receptor blockade in the parasympathetic nervous system leads to a range of clinical effects including mydriasis, increased heart rate, bronchodilation, reduced secretions, and antispasmodic effects in the GI and genitourinary tract.
- Antimuscarinic medications for specific indications have been formulated to optimize certain antagonistic effects, while minimizing others to avoid side effects. Examples include *ipratropium* for COPD, *scopolamine* for PONV, and *tolterodine* for urinary incontinence.
- Adverse effects of muscarinic antagonists include dry mouth, mydriasis, confusion, urinary retention, constipation, and blurred vision.
- Neuromuscular blocking agents act as antagonists at nicotinic receptors in the somatic nervous system to induce skeletal muscle paralysis. These agents are used to facilitate intubation and surgery and to assist in the care of critically ill patients such as those with severe brain or lung injury.
- Neuromuscular blocking agents are classified as depolarizing or nondepolarizing. *Succinylcholine* is a depolarizing NMB that binds to the nicotinic receptor in skeletal muscle and acts like ACh to depolarize the NMJ. Unlike ACh, *succinylcholine* remains bound to the receptor for a longer time, thereby providing sustained depolarization of the muscle cell and flaccid paralysis. Nondepolarizing NMBs (*cisatracurium*, *mivacurium, pancuronium, rocuronium, vecuronium*) competitively block ACh at the nicotinic receptors in skeletal muscle, thus preventing depolarization of the muscle cell membrane and inhibiting subsequent muscular contraction.

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STUDY QUESTIONS

Choose the ONE best answer.

5.1 During an ophthalmic surgical procedure, the surgeon wanted to constrict the pupil using a miotic drug. However, he

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accidently used another drug that caused dilation of the pupil (mydriasis). Which drug was most likely used?

A. Acetylcholine
B. Pilocarpine
C. Cyclopentolate
D. Bethanechol

Correct answer = C. Muscarinic agonists such as ACh, pilocarpine, and bethanechol contract the circular muscles of the iris sphincter and cause constriction of the pupil (miosis), whereas muscarinic antagonists such as cyclopentolate prevent contraction of the circular muscles of the iris and cause dilation of the pupil (mydriasis).

5.2 A 54-year-old woman who is noncompliant with medications was recently diagnosed with chronic obstructive pulmonary disease (COPD). Her physician would like to prescribe an inhaled anticholinergic that is dosed once or twice daily. Which drug is most appropriate for this patient?

A. Atropine
B. Ipratropium
C. Tiotropium
D. Albuterol

Correct answer = C. The physician should prescribe a long-acting muscarinic antagonist (LAMA) so that the patient has to inhale the medication only 1 or 2 times daily. Tiotropium is a LAMA, whereas ipratropium is a SAMA. Atropine is a muscarinic antagonist, but it is not indicated for conditions such as asthma or COPD and is not available as inhaled formulation. Albuterol does cause bronchodilation, but it is a short-acting β agonist, not an anticholinergic.

5.3 Which is the most effective drug for motion sickness for a person planning to go on a cruise?

A. Ipratropium
B. Fesoterodine

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C. Scopolamine
D. Tropicamide

Correct answer = C. All muscarinic antagonists (anticholinergic drugs) listed are theoretically useful as antimotion sickness drugs; however, scopolamine is the most effective in preventing motion sickness. Ipratropium has only pulmonary indications, tropicamide mostly has ophthalmic uses, and fesoterodine is used for overactive bladder.

5.4 Which is correct regarding ganglion-blocking drugs?

A. Blockade of sympathetic ganglia could result in reduced blood pressure.
B. Blockade of parasympathetic ganglia could result in reduced heart rate.
C. Nicotine is a nondepolarizing ganglion blocker.
D. Atropine is a nondepolarizing ganglion blocker.

Correct answer = A. Selective blockade (in theory) of the sympathetic ganglion causes reduction in norepinephrine release and, therefore, reduction in heart rate and blood pressure. Selective blockade (in theory) of the parasympathetic ganglion causes reduction in ACh release and an increase in heart rate. Receptors at both sympathetic and parasympathetic ganglia are of the nicotinic type. Nicotine is an agonist at nicotinic receptors and produces a depolarizing block in the ganglia. Atropine is a muscarinic antagonist and has no effect on the nicotinic receptors found in the ganglia.

5.5 Which of the following stimulates release of the-neurotransmitters serotonin, GABA, glutamate, and acetylcholine?

A. Organophosphate pesticides
B. Atropine
C. Succinylcholine
D. Nicotine

Correct answer = D. Nicotine is a ganglionic blocker whose stimulatory effects are complex and result from increased release of neurotransmitters due to

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effects on both sympathetic and parasympathetic ganglia. Atropine acts to block the muscarinic receptors. Organophosphate pesticides stimulate the muscarinic receptors. Succinylcholine acts to block acetylcholine at the neuromuscular junction.

5.6 A hospitalized patient is diagnosed with symptomatic bradycardia. Which of the following would be the most appropriate agent to treat the bradycardia?

A. Ipratropium
B. Atropine
C. Vecuronium
D. Solifenacin

Correct answer = B. Following normal doses of atropine there is a blocking of the M_2 receptors in the SA node leading to an increase in heart rate. Ipratropium is indicated for bronchodilation, is not well absorbed, and thus would not be a good agent. Vecuronium is a neuromuscular blocking agent and would not be expected to increase heart rate. Solifenacin is indicated for the treatment of overactive bladder.

5.7 A 38-year-old man receives an intramuscular injection of scopolamine to relax his intestine for colonoscopy. Which of the following effects would this patient most likely experience after administration of the drug?

A. Urinary incontinence
B. Increased salivation
C. Bronchospasm
D. Increased heart rate

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Correct answer = D. Scopolamine is an antimuscarinic drug. It blocks M_2 receptors mainly on sinoatrial and atrioventricular nodes to decrease the vagal control to the heart. This can lead to an increased heart rate that can cause a conscious awareness of the heart beat (also known as palpitations). A is incorrect as antimuscarinic effects would lead to urinary retention not incontinence. B is incorrect as the antimuscarinic effects would lead to

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decreased salivation. C is incorrect as the antimuscarinic effects would lead to bronchodilation.

5.8 A patient needs to be intubated quickly and the clinician would like to use a medication to paralyze the patient that has a rapid onset of action but does not last long. Which of the following would be the best choice?

A. Pancuronium
B. Cisatracurium
C. Vecuronium
D. Succinylcholine

Correct answer = D. Succinylcholine has the quickest onset of about 1 minute and the shortest duration of about 5 to 8 minutes. Pancuronium, cis-atracurium, and vecuronium all take longer to act and have longer durations of action.

5.9 An ICU patient with severe lung injury requires a neuromuscular blocking agent to assist in his ventilator management. He is currently suffering from liver disease. Which nondepolarizing neuromuscular blocker is the best choice for this patient?

A. Cisatracurium
B. Succinylcholine
C. Vecuronium
D. Rocuronium

Correct answer = A. Cisatracurium is cleared by organ-independent metabolism (Hofmann elimination). Succinylcholine is a depolarizing neuromuscular blocking agent. Vecuronium and rocuronium are hepatically metabolized and the patient has liver disease.

5.10A patient is being initiated on therapy for bladder spasms. The patient is also taking medication that inhibits the CYP 3A4 metabolic pathway. Which of the following would be the best agent for treating bladder spasms in this patient?

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A. Trospium
B. Tolterodine
C. Oxybutynin
D. Darifenacin

Correct answer = A. Trospium is thought to be metabolized via ester hydrolysis and thus less likely to be impacted by CYP 3A4 metabolic pathway interactions than the other agents for bladder spasm. The other agents are all metabolized to some extent through the CYP 3A4 metabolic pathway.

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6

Adrenergic Agonists

Reem Kais Jan, Rajan Radhakrishnan

I. OVERVIEW

The adrenergic drugs affect receptors that are stimulated by norepinephrine (noradrenaline) or epinephrine (adrenaline). These receptors are known as adrenergic receptors or adrenoceptors. Drugs that activate adrenergic receptors are termed sympathomimetics, and drugs that block activation of adrenergic receptors are termed sympatholytics. Some sympathomimetics directly activate adrenergic receptors (direct-acting agonists), while others act indirectly by enhancing release or blocking reuptake of norepinephrine (indirect-acting agonists). This chapter describes agents that either directly or indirectly stimulate adrenoceptors (Figure 6.1). Sympatholytic drugs are discussed in Chapter 7.

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DIRECT-ACTING AGENTS

Albuterol PROAIR, PROVENTIL, VENTOLIN
Arformoterol BROVANA
Clonidine CATAPRES, DURACLON
*Dobutamine** GENERIC ONLY
*Dopamine** GENERIC ONLY
*Epinephrine** ADRENACLICK, ADRENALIN, EPIPEN
Formoterol FORADIL, PERFOROMIST
Guanfacine INTUNIV
Indacaterol ARCAPTA
*Isoproterenol** ISUPREL
Levalbuterol XOPONEX
Metaproterenol GENERIC ONLY
Midodrine GENERIC ONLY
Mirabegron MYRBETRIQ
Naphazoline GENERIC ONLY
*Norepinephrine** LEVOPHED
Olodaterol STRIVERDI
Oxymetazoline AFRIN
Phenylephrine NEO-SYNEPHRINE, SUDAFED PE
Salmeterol SEREVENT
Tetrahydrozoline VISINE
Terbutaline GENERIC ONLY
Vibegron GEMTESA

INDIRECT-ACTING AGENTS

Amphetamine ADDERALL, MYDAYIS
Cocaine GENERIC ONLY

DIRECT AND INDIRECT ACTING (mixed action) AGENTS

Ephedrine AKOVAZ, EMERPHED
Pseudoephedrine GENAPHED, SUDAFED

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Figure 6.1 Summary of adrenergic agonists.Agents marked with an *asterisk* (*) are catecholamines.

II. THE ADRENERGIC NEURON

Adrenergic neurons release norepinephrine as the primary neurotransmitter. These neurons are found in the central nervous system (CNS) and in the sympathetic nervous system in the periphery where they serve as links between ganglia and the effector organs. Adrenergic drugs act on adrenergic receptors, located either presynaptically on the neuron or postsynaptically on the effector organ (Figure 6.2).

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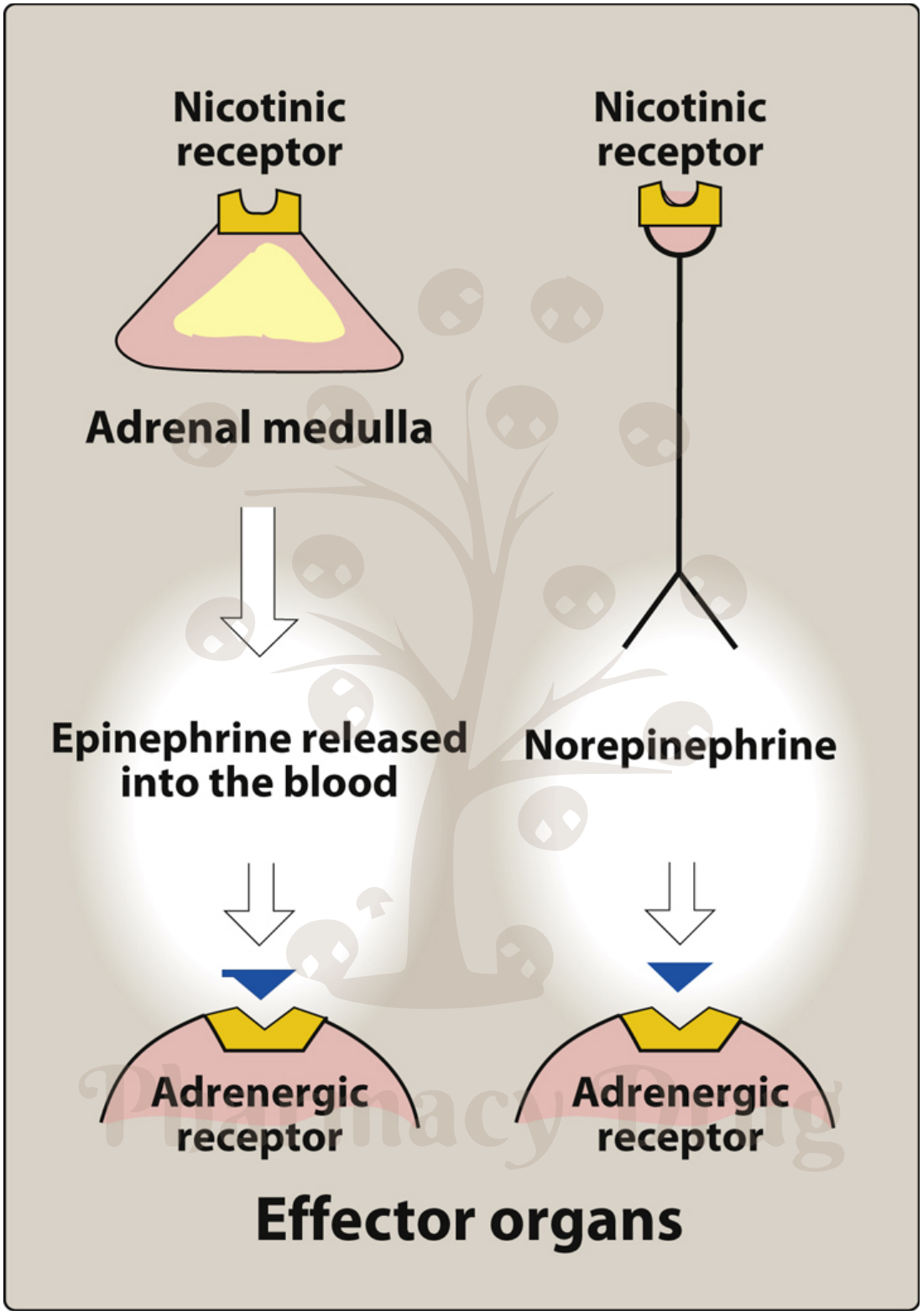

Figure 6.2 Sites of actions of adrenergic agonists.

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A. Neurotransmission at adrenergic neurons

Neurotransmission in adrenergic neurons closely resembles that described for the cholinergic neurons (see Chapter 4), except that norepinephrine is the neurotransmitter instead of acetylcholine. Neurotransmission involves the following steps: synthesis, storage, release, and receptor binding of norepinephrine, followed by removal of the neurotransmitter from the synaptic space (Figure 6.3).

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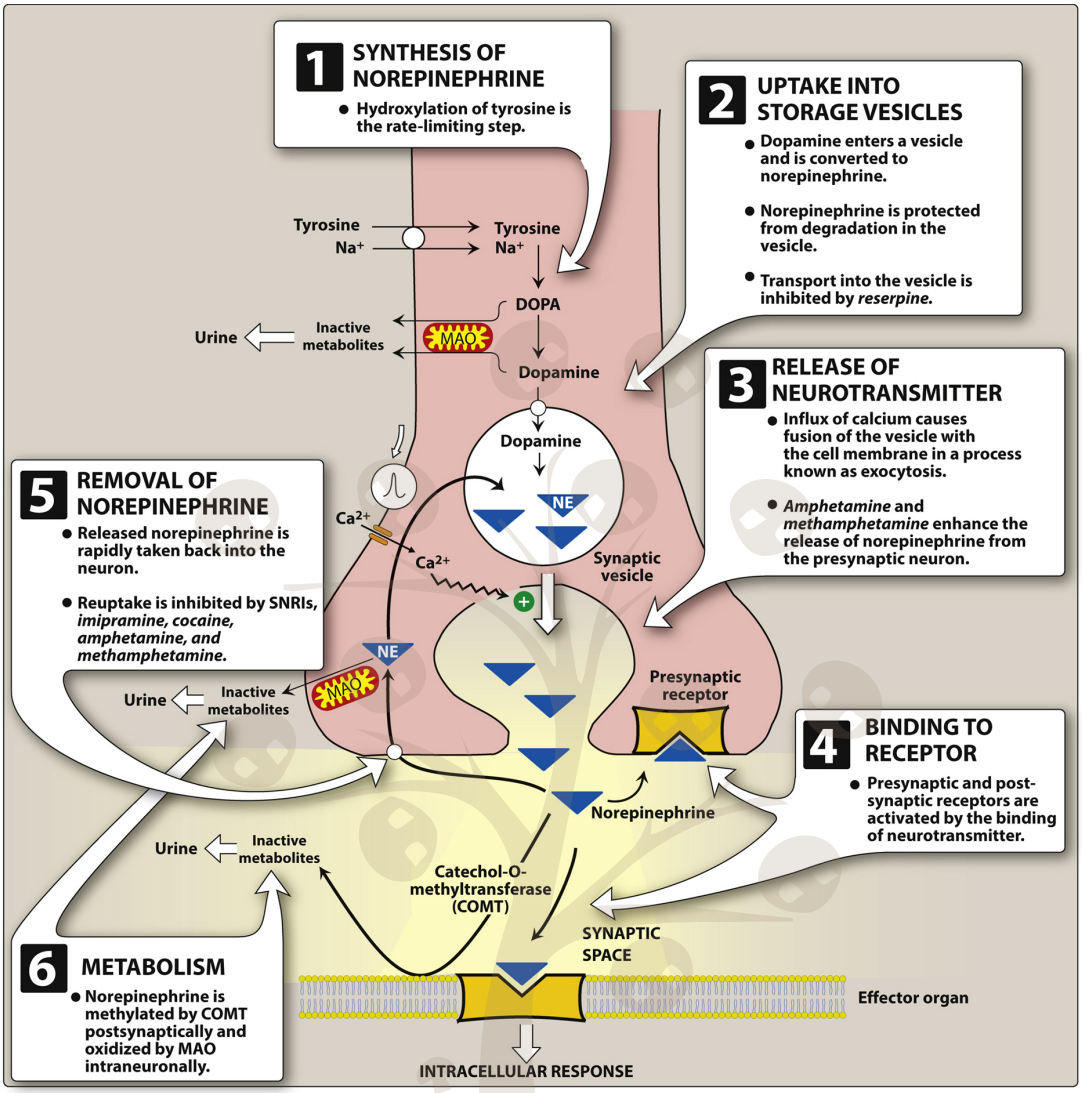

Figure 6.3 Synthesis and release of norepinephrine from the adrenergic neuron.DOPA = dihydroxyphenylalanine; MAO = monoamine oxidase; NE = norepinephrine; SNRI = serotonin–norepinephrine reuptake inhibitor.

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1.Synthesis of norepinephrine: Tyrosine is transported by a carrier into the adrenergic neuron, where it is hydroxylated to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase. This is the rate-limiting step in the formation of norepinephrine. DOPA is then decarboxylated by the enzyme aromatic l-amino acid decarboxylase to form dopamine in the presynaptic neuron.

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2. Storage of norepinephrine in vesicles: Dopamine is then transported into synaptic vesicles by an amine transporter system. This carrier system is blocked by *reserpine* (see Chapter 7). Next, *dopamine* is hydroxylated to form norepinephrine by the enzyme dopamine β-hydroxylase.

3. Release of norepinephrine: An action potential arriving at the nerve junction triggers an influx of calcium ions from the extracellular fluid into the cytoplasm of the neuron. The increase in calcium causes synaptic vesicles to fuse with the cell membrane and to undergo exocytosis and expel their contents into the synapse.

4. Binding to receptors: Norepinephrine released from the synaptic vesicles diffuses into the synaptic space and binds to postsynaptic receptors on the effector organ or to presynaptic receptors on the nerve ending. Binding of norepinephrine to receptors triggers a cascade of events within the cell, resulting in the formation of intracellular second messengers that act as links (transducers) in the communication between the neurotransmitter and the action generated within the effector cell. Adrenergic receptors use both the cyclic adenosine monophosphate (cAMP) second messenger system and the phosphatidylinositol cycle to transduce the signal into a physiological or pharmacological effect. Norepinephrine also binds to presynaptic receptors (mainly α_2 subtype) that inhibit the release of the neurotransmitter.

5. Removal of norepinephrine: Once in the synaptic space, norepinephrine may (1) diffuse into the systemic circulation, (2) be metabolized to inactive metabolites by catechol-O-methyltransferase (COMT) in the synaptic space, or (3) undergo reuptake back into the neuron. The reuptake by the neuronal membrane involves a sodium–chloride (Na^+/Cl^-)–dependent norepinephrine transporter that can be inhibited by tricyclic antidepressants, such as *imipramine*; by serotonin–norepinephrine reuptake inhibitors such as *duloxetine*; or by

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cocaine, and to a lesser extent by *amphetamine, methamphetamine,* and *methylphenidate* (see Chapter 22). Reuptake of norepinephrine into the presynaptic neuron is the primary mechanism for termination of its effects.

6.Potential fates of recaptured norepinephrine: Once norepinephrine reenters the adrenergic neuron, it may be taken up into synaptic vesicles via the amine transporter system and be sequestered for release by another action potential or it may persist in a protected pool in the cytoplasm. Alternatively, norepinephrine can be oxidized by monoamine oxidase (MAO) present in neuronal mitochondria.

B. Adrenergic receptors (adrenoceptors)

In the sympathetic nervous system, several classes of adrenoceptors can be distinguished pharmacologically. Two main families of receptors, designated α and β, are classified based on their differential responses to the adrenergic agonists *epinephrine*, *norepinephrine*, and *isoproterenol.* Both the α and β receptor types have a number of specific receptor subtypes. Alterations in the primary structure of the receptors influence their affinity for various agents.

1.α-Adrenoceptors: The α-adrenoceptors show a weak response to the synthetic agonist *isoproterenol*, but they are responsive to the naturally occurring catecholamines *epinephrine* and *norepinephrine* (Figure 6.4A). For α receptors, the rank order of potency and affinity is *epinephrine* ≥ *norepinephrine* >> *isoproterenol.* The α-adrenoceptors are divided into two subtypes, α_1 and α_2, based on their affinities for α agonists and antagonists. For example, α_1 receptors have a higher affinity for *phenylephrine* than α_2 receptors. Conversely, the drug *clonidine* selectively binds to α_2 receptors and has less effect on α_1 receptors.

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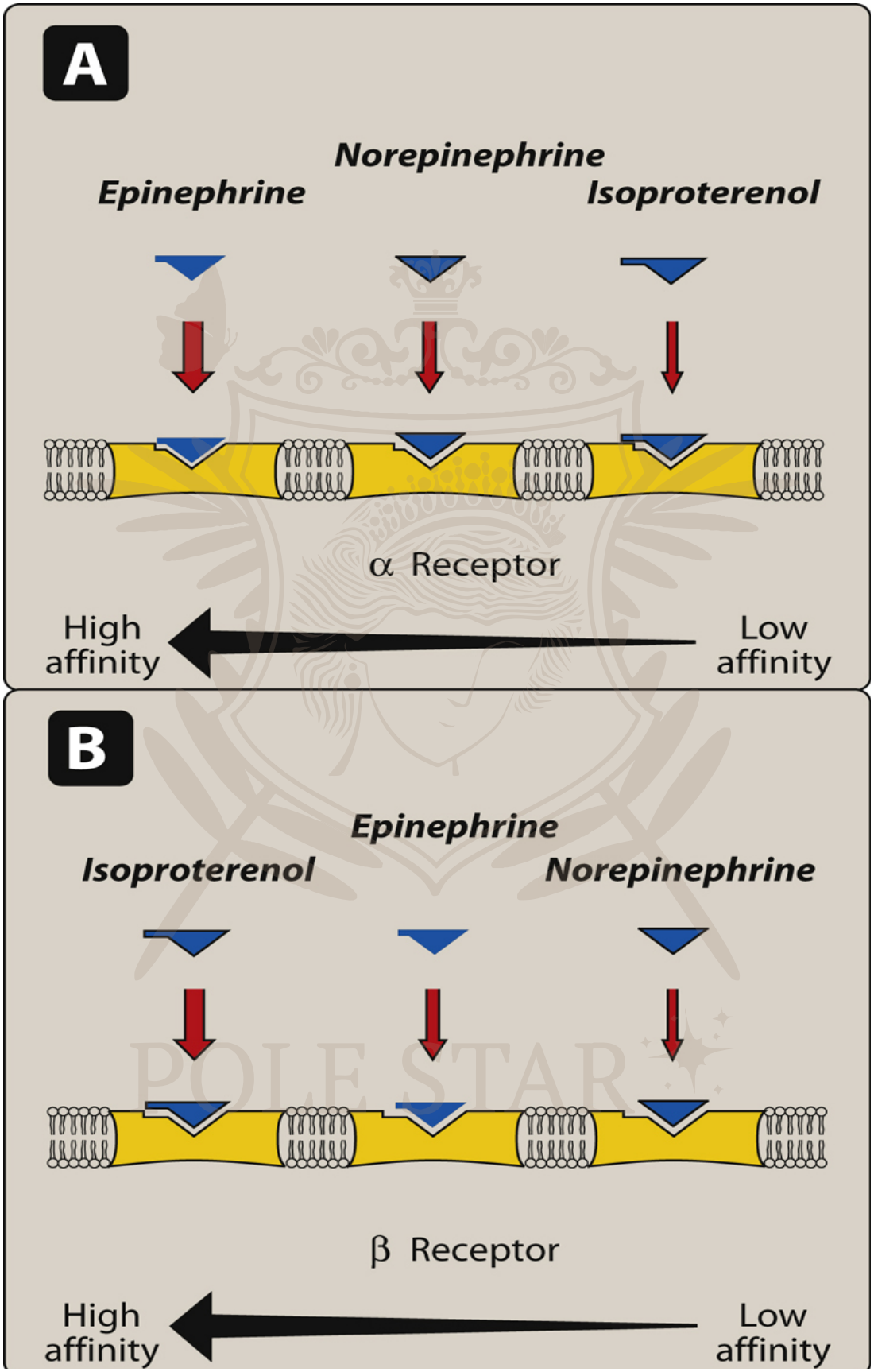
A
Norepinephrine
Epinephrine
Isoproterenol
α Receptor
High affinity
Low affinity
B
Epinephrine
Isoproterenol
Norepinephrine
β Receptor
High affinity
Low affinity

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Figure 6.4 Types of adrenergic receptors.**A.** α-Adrenoceptors. **B.** β-Adrenoceptors.

a. α_1 Receptors: These receptors are present on the postsynaptic membrane of the effector organs and mediate many of the classic effects involving constriction of vascular smooth muscle. Activation of α_1 receptors initiates a series of reactions through the G protein activation of phospholipase C, ultimately resulting in the generation of second messengers inositol-1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 initiates the release of Ca^{2+} from the endoplasmic reticulum into the cytosol, and DAG activates other proteins within the cell (Figure 6.5).

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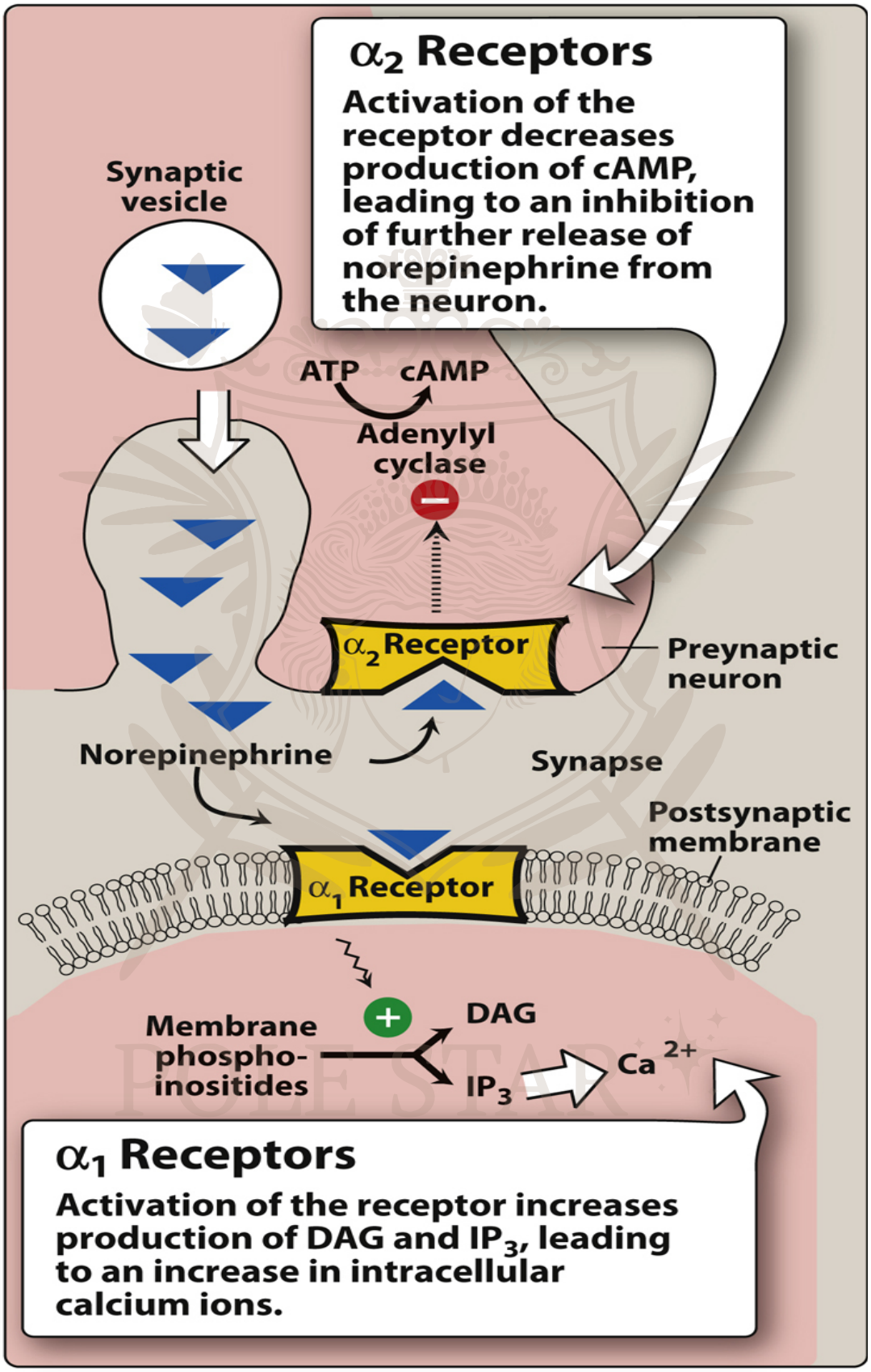
α2 Receptors
Activation of the receptor decreases production of cAMP, leading to an inhibition of further release of norepinephrine from the neuron.
Synaptic vesicle
ATP
cAMP
Adenylyl cyclase
α2 Receptor
Preynaptic neuron
Norepinephrine
Synapse
Postsynaptic membrane
α1 Receptor
Membrane phospho-inositides
DAG
IP3
Ca 2+
α1 Receptors
Activation of the receptor increases production of DAG and IP3, leading to an increase in intracellular calcium ions.

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Figure 6.5 Second messengers mediate the effects of α receptors.ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; DAG = diacylglycerol; IP_3 = inositol trisphosphate.

b. α_2 Receptors: These receptors are located primarily on sympathetic presynaptic nerve endings and control the release of norepinephrine. When a sympathetic adrenergic nerve is stimulated, a portion of the released norepinephrine "circles back" and reacts with α_2 receptors on the presynaptic membrane (Figure 6.5). Stimulation of α_2 receptors causes feedback inhibition and inhibits further release of norepinephrine from the stimulated adrenergic neuron. This inhibitory action serves as a local mechanism for modulating norepinephrine output when there is high sympathetic activity. [Note: In this instance, by inhibiting further output of norepinephrine from the adrenergic neuron, these receptors are acting as inhibitory autoreceptors.] α_2 Receptors are also found on presynaptic parasympathetic neurons. Norepinephrine released from a presynaptic sympathetic neuron can diffuse to and interact with these receptors, inhibiting acetylcholine release. [Note: In these instances, these receptors are behaving as inhibitory heteroreceptors.] This is another mechanism to modulate autonomic activity locally. In contrast to α_1 receptors, the effects of binding at α_2 receptors are mediated by inhibition of adenylyl cyclase, resulting in a fall in the levels of intracellular cAMP.

c. Further subdivisions: The α_1 and α_2 receptors are further divided into α_{1A}, α_{1B}, α_{1C}, and α_{1D} and into α_{2A}, α_{2B}, and α_{2C}. This extended classification is necessary for understanding the selectivity of some drugs. For example,

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tamsulosin is a selective α_{1A} antagonist that is used to treat benign prostatic hyperplasia. The drug has fewer cardiovascular side effects because it targets α_{1A} subtype receptors found primarily in the urinary tract and prostate gland and does not affect the α_{1B} subtype found in the blood vessels.

2.β-Adrenoceptors: Responses of β receptors differ from those of α receptors and are characterized by a strong response to *isoproterenol*, with less sensitivity to *epinephrine* and *norepinephrine* (Figure 6.4B). For β receptors, the rank order of potency is *isoproterenol* > *epinephrine* > *norepinephrine.* The β-adrenoceptors can be subdivided into three major subgroups, β_1, β_2, and β_3, based on their affinities for adrenergic agonists and antagonists. β_1 Receptors have approximately equal affinities for *epinephrine* and *norepinephrine*, whereas β_2 receptors have a higher affinity for *epinephrine* than for *norepinephrine.* Thus, tissues with a predominance of β_2 receptors (such as the vasculature of skeletal muscle and bronchial smooth muscle) are particularly responsive to the effects of circulating epinephrine released by the adrenal medulla. Binding of a neurotransmitter at any of the three types of β receptors results in activation of adenylyl cyclase and increased concentrations of cAMP within the cell.

3.Distribution of receptors: Adrenergically innervated organs and tissues usually have a predominant type of receptor. For example, tissues such as the vasculature of skeletal muscle have both α_1 and β_2 receptors, but the β_2 receptors predominate. Other tissues may have one type of receptor almost exclusively. For example, the heart contains predominantly β_1 receptors.

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4.Characteristic responses mediated by adrenoceptors: It is useful to organize the physiologic responses to adrenergic stimulation according to receptor type, because many drugs preferentially stimulate or block one type of receptor. Figure 6.6 summarizes the most prominent effects mediated by the adrenoceptors. As a generalization, stimulation of α_1 receptors characteristically produces vasoconstriction (particularly in skin and abdominal viscera) and an increase in total peripheral resistance and subsequent increase in blood pressure. Stimulation of β_1 receptors characteristically causes cardiac stimulation (increase in heart rate and contractility), whereas stimulation of β_2 receptors produces vasodilation (in skeletal muscle vascular beds) and bronchial smooth muscle relaxation. β_3 Receptors are involved in lipolysis and also mediate relaxant effects in the detrusor muscle of the bladder.

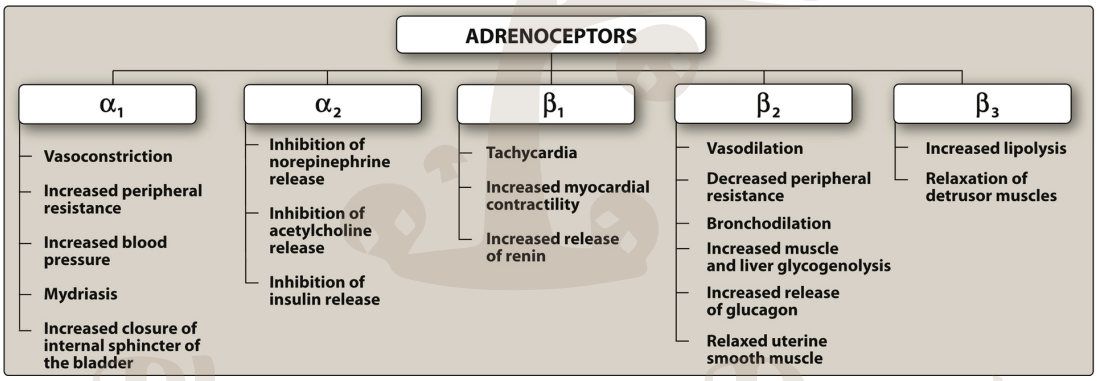

Figure 6.6 Major effects mediated by α- and β-adrenoceptors.

5.Desensitization of receptors: Prolonged exposure to the catecholamines reduces the responsiveness of these receptors, a phenomenon known as desensitization. Three mechanisms have been suggested to explain this phenomenon: (1) sequestration of the receptors so that they

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are unavailable for interaction with the ligand; (2) downregulation, that is, a disappearance of the receptors either by destruction or by decreased synthesis; and (3) an inability to couple to G protein (uncoupling), because the receptor has been phosphorylated on the cytoplasmic side.

III. CHARACTERISTICS OF ADRENERGIC AGONISTS

Most adrenergic drugs are derivatives of β-phenylethylamine. Substitutions on the benzene ring or on the ethylamine side chains produce a variety of compounds with varying abilities to differentiate between α and β receptors and to penetrate the CNS. Two important structural features of these drugs are (1) the number and location of OH substitutions on the benzene ring and (2) the nature of the substituent on the amino nitrogen (Figure 6.7).

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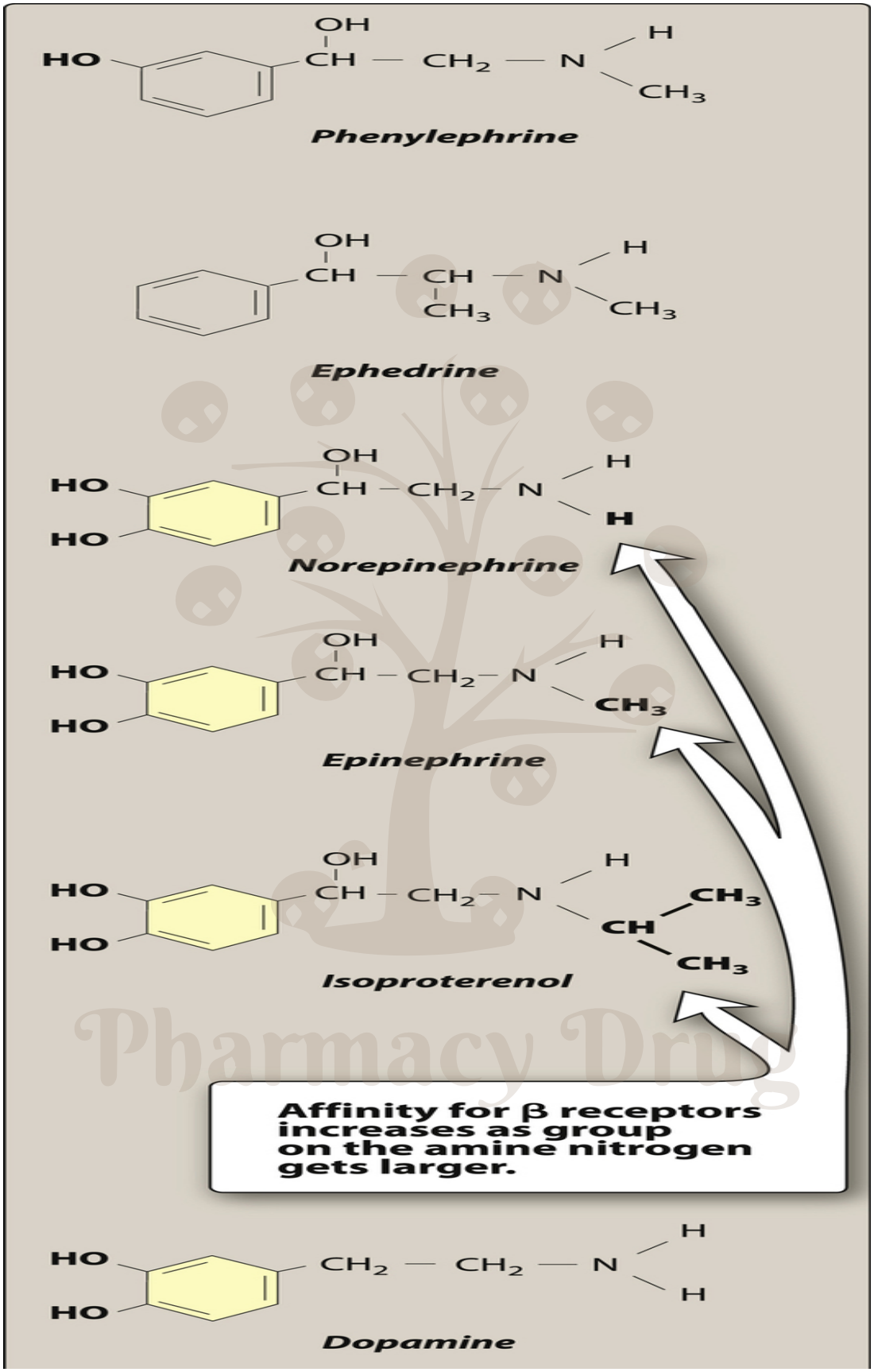

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Figure 6.7 Structures of several important adrenergic agonists.Drugs containing the catechol ring (catecholamines) are shown in *yellow*.

A. Catecholamines

Sympathomimetic amines that contain the 3,4-dihydroxybenzene group (such as *epinephrine*, *norepinephrine*, *isoproterenol*, and *dopamine*) are called catecholamines. These compounds share the following properties:

1. **High potency:** Catecholamines show the highest potency in directly activating α or β receptors.
2. **Rapid inactivation:** Catecholamines are metabolized by COMT postsynaptically and by MAO intraneuronally, by COMT and MAO in the gut wall, and by MAO in the liver. Thus, catecholamines have only a brief period of action when given parenterally, and they are inactivated (ineffective) when administered orally.
3. **Poor penetration into the CNS:** Catecholamines are polar and, therefore, do not readily penetrate into the CNS. Nevertheless, most catecholamines have some clinical effects (anxiety, tremor, and headaches) that are attributable to action on the CNS.

B. Noncatecholamines

Compounds lacking the catechol hydroxyl groups have longer half-lives, because they are not inactivated by COMT. These include *phenylephrine*, *ephedrine* (Figure 6.7), and *amphetamine* (see Chapter 22). These agents are poor substrates for MAO, an important route of metabolism, and thus show a prolonged duration of action. Increased lipid solubility of many of the noncatecholamines (due to lack of polar hydroxyl groups) permits greater access to the CNS.

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C. Substitutions on the amine nitrogen

The nature of the substituent on the amine nitrogen is important in determining β selectivity of the adrenergic agonist. For example, *epinephrine*, with a $–CH_3$ substituent on the amine nitrogen, is more potent at β receptors than *norepinephrine*, which has an unsubstituted amine, but less potent than *isoproterenol*, which has an isopropyl substituent $–CH(CH_3)_2$ on the amine nitrogen (Figure 6.7). *Isoproterenol* is a strong β agonist with little α agonist activity (Figure 6.4).

D. Mechanism of action of adrenergic agonists

1. **Direct-acting agonists:** These drugs act directly on α or β receptors, producing effects similar to those that occur following the release of norepinephrine from the sympathetic nerves or release of epinephrine from the adrenal medulla (Figure 6.8). Examples of direct-acting agonists include *epinephrine*, *norepinephrine*, *isoproterenol*, *dopamine*, and *phenylephrine*.

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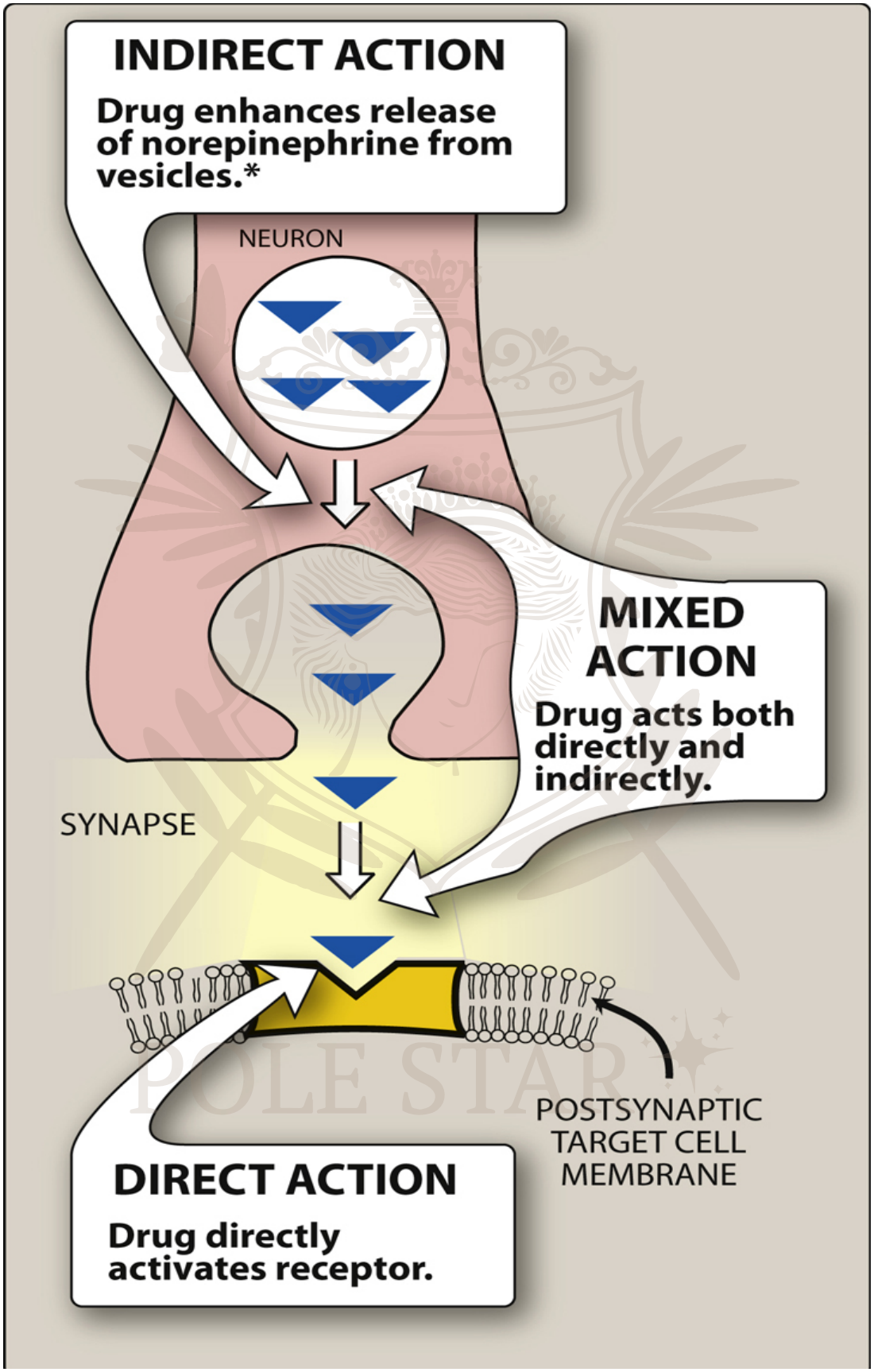
INDIRECT ACTION
Drug enhances release of norepinephrine from vesicles.*
NEURON
MIXED ACTION
Drug acts both directly and indirectly.
SYNAPSE
POSTSYNAPTIC TARGET CELL MEMBRANE
DIRECT ACTION
Drug directly activates receptor.

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Figure 6.8 Sites of action of direct-, indirect-, and mixed-acting adrenergic agonists.*Indirect-acting agonists may also block reuptake of norepinephrine into the presynaptic neuron.

2. **Indirect-acting agonists:** These agents may block the reuptake of norepinephrine or cause the release of norepinephrine from the cytoplasmic pools or vesicles of the adrenergic neuron (Figure 6.8). The norepinephrine then traverses the synapse and binds to α or β receptors. Examples of reuptake inhibitors and agents that cause norepinephrine release include *cocaine* and *amphetamine*, respectively.

3. **Mixed-acting agonists:** *Ephedrine* and its stereoisomer, *pseudoephedrine*, both stimulate adrenoceptors directly and enhance release of *norepinephrine* from the adrenergic neuron (Figure 6.8).

IV. DIRECT-ACTING ADRENERGIC AGONISTS

In general, direct-acting agonists bind to adrenergic receptors on effector organs without interacting with the presynaptic neuron. [Note: An exception are the α_2 agonists (for example, *clonidine*), which exert effects through binding to the presynaptic neuron.] As a group, these agents are widely used in clinical practice. The direct-acting endogenous catecholamines (*epinephrine*, *norepinephrine*, *dopamine*) are reviewed first, followed by the synthetic α_1 and α_2 agonists, and then the synthetic β_1, β_2, and β_3 agonists.

A. Epinephrine

Epinephrine [ep-i-NEF-rin] is one of the few endogenous catecholamines commonly used as drug therapy in clinical practice. In the adrenal medulla, norepinephrine is methylated to

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yield epinephrine, which is stored in chromaffin cells along with norepinephrine. Upon stimulation, the adrenal medulla releases about 80% epinephrine and 20% norepinephrine directly into the circulation. *Epinephrine* interacts with both α and β receptors. At low doses, β effects (vasodilation) on the vascular system predominate, whereas at high doses, α effects (vasoconstriction) are the strongest.

1.Actions

a. Cardiovascular: The major actions of *epinephrine* are on the cardiovascular system. *Epinephrine* strengthens the contractility of the myocardium (positive inotrope: β_1 action) and increases its rate of contraction (positive chronotrope: β_1 action), leading to an increase in cardiac output. These effects increase oxygen demand in the myocardium. *Epinephrine* activates β_1 receptors in the kidney to cause renin release. Renin is an enzyme involved in the production of angiotensin II, a potent vasoconstrictor. *Epinephrine* constricts arterioles in the skin, mucous membranes, and viscera (α effects), and it dilates vessels going to the liver and skeletal muscle (β_2 effects). These combined effects result in a decrease in renal blood flow. Therefore, the cumulative effect is an increase in systolic blood pressure, coupled with a slight decrease in diastolic pressure due to β_2 receptor–mediated vasodilation in the skeletal muscle vascular bed (Figure 6.9).

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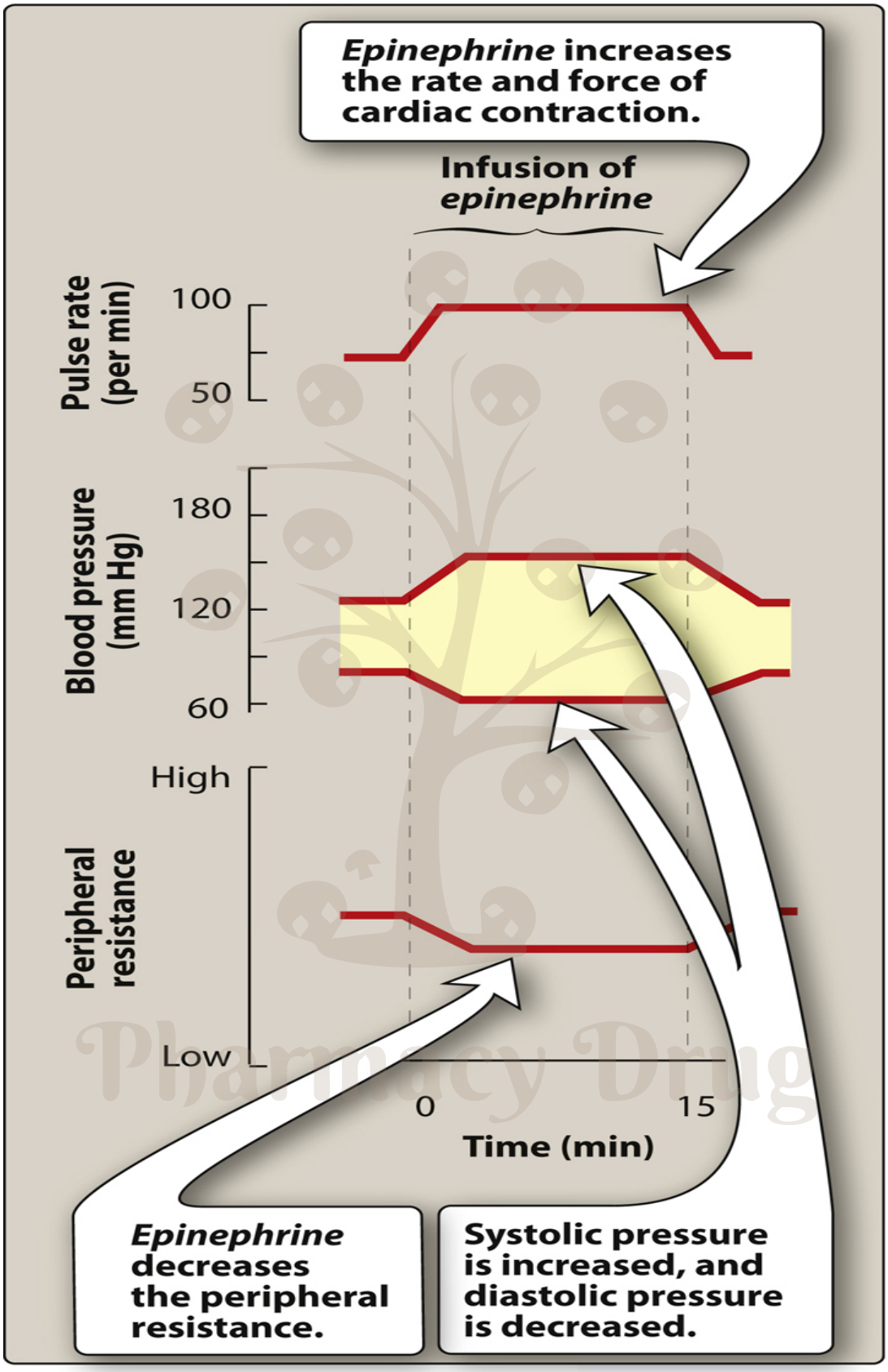

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Figure 6.9 Cardiovascular effects of intravenous infusion of low doses of *epinephrine*.Modified from M. J.Allwood , A. F.Cobbold , and J.Ginsburg . Peripheral vascular effects of noradrenaline, isopropylnoradrenaline and dopamine. *Br. Med. Bull*. 19: 132 (1963).

b. Respiratory: *Epinephrine* causes powerful bronchodilation by acting directly on bronchial smooth muscle (β_2 action). It also inhibits the release of allergic mediators such as histamine from mast cells.

c. Hyperglycemia: *Epinephrine* has a significant hyperglycemic effect because of increased glycogenolysis in the liver (β_2 effect), increased release of glucagon (β_2 effect), and a decreased release of *insulin* (α_2 effect; see Figure 6.6).

2.Therapeutic uses

a. Bronchospasm: *Epinephrine* is the primary drug used in the emergency treatment of respiratory conditions when bronchoconstriction has resulted in diminished respiratory function. A few minutes after intramuscular or subcutaneous administration, respiratory function greatly improves.

b. Anaphylactic shock: *Epinephrine* is the drug of choice for the treatment of type I hypersensitivity reactions (including anaphylaxis) in response to allergens and can be lifesaving in this setting. It is usually supplied in the form of autoinjectors for use by patients prone to severe allergic reactions.

c. Cardiac arrest: *Epinephrine* may be used to restore cardiac rhythm in patients with cardiac arrest.

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d. Adjuvant in local anesthesia: Local anesthetic solutions may contain low concentrations (for example, 1:100,000 parts) of *epinephrine. Epinephrine* greatly increases the duration of local anesthesia by producing vasoconstriction at the site of injection. *Epinephrine* also reduces systemic absorption of the local anesthetic and promotes local hemostasis.

e. Intraocular surgery: *Epinephrine* is used in the induction and maintenance of mydriasis during intraocular surgery.

3.Pharmacokinetics: *Epinephrine* has a rapid onset but a brief duration of action (due to rapid degradation). The preferred route for anaphylaxis in the outpatient setting is intramuscular (anterior thigh) due to rapid absorption. In emergencies, *epinephrine* is given intravenously (IV) for the most rapid onset of action. It may also be given subcutaneously, by endotracheal tube, or by inhalation (Figure 6.10). It is rapidly metabolized by MAO and COMT, and the metabolites metanephrine and vanillylmandelic acid are excreted in urine.

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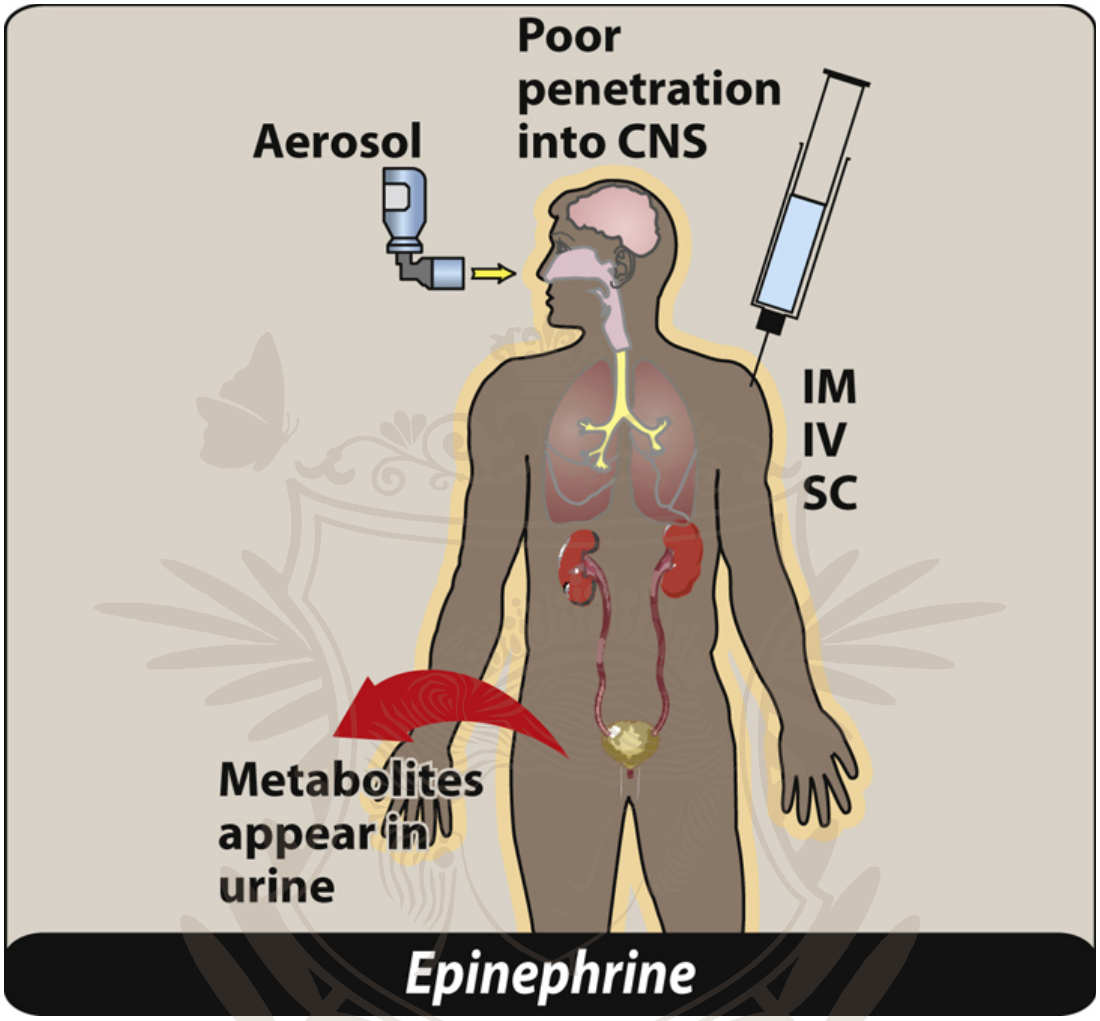

Figure 6.10 Pharmacokinetics of *epinephrine*.CNS = central nervous system.

4.Adverse effects: *Epinephrine* can produce adverse CNS effects that include anxiety, fear, tension, headache, and tremor. It can trigger cardiac arrhythmias or angina, particularly if the patient has coronary artery disease or hypertension. *Epinephrine* can also induce pulmonary edema due to increased afterload caused by vasoconstrictive properties of the drug. Patients with hyperthyroidism may have an enhanced response to *epinephrine*, and, therefore, the dose must be reduced in these individuals. Inhalation anesthetics also sensitize the heart to the effects of *epinephrine*, which

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may lead to tachycardia. *Epinephrine* increases the release of endogenous stores of glucose. In patients with diabetes, dosages of *insulin* may have to be increased. In patients taking nonselective β-blockers, vasodilatory effects of *epinephrine* on β_2 receptors may be blocked, leaving α receptor stimulation unopposed. This may lead to increased peripheral resistance and increased blood pressure.

Clinical Application 6.1 Use of Epinephrine Autoinjectors for Anaphylaxis

Epinephrine is the drug of choice for management of life-threatening allergic reactions (anaphylaxis). Anaphylactic reactions may occur within seconds to minutes following exposure to a triggering allergen. Some of the most common triggers for anaphylaxis include food allergies (for example, nuts, shellfish, eggs), insect stings (bees, wasps, and fire ants), and other allergic triggers, such as latex. The flood of mediators (histamine and others) released in response to the allergen causes a reduction in blood pressure (hypotension), increased heart rate (tachycardia), and bronchoconstriction, which can cause difficulty in breathing.

Anaphylactic reactions can occur in a variety of places (for example, in restaurants, on the school playground, or on an airplane), and it is essential that patients with known severe allergic reactions carry *epinephrine* with them, since timely administration can be life-saving. *Epinephrine* is supplied as an autoinjector (a portable device resembling a pen that allows the patient to self-administer the injection) for use in these cases. These devices are designed for intramuscular administration, and the patient and close family members or caregivers should be trained on appropriate administration of the *epinephrine* autoinjector. Patients should be instructed to inject into the muscle in the anterolateral thigh (the middle of the outer thigh). The injection may be administered through clothing, if needed. Following administration, the device should be held in place for 2 to 10 seconds (time varies per type of injector used), and emergency services should be contacted for assistance with further management of the anaphylaxis.

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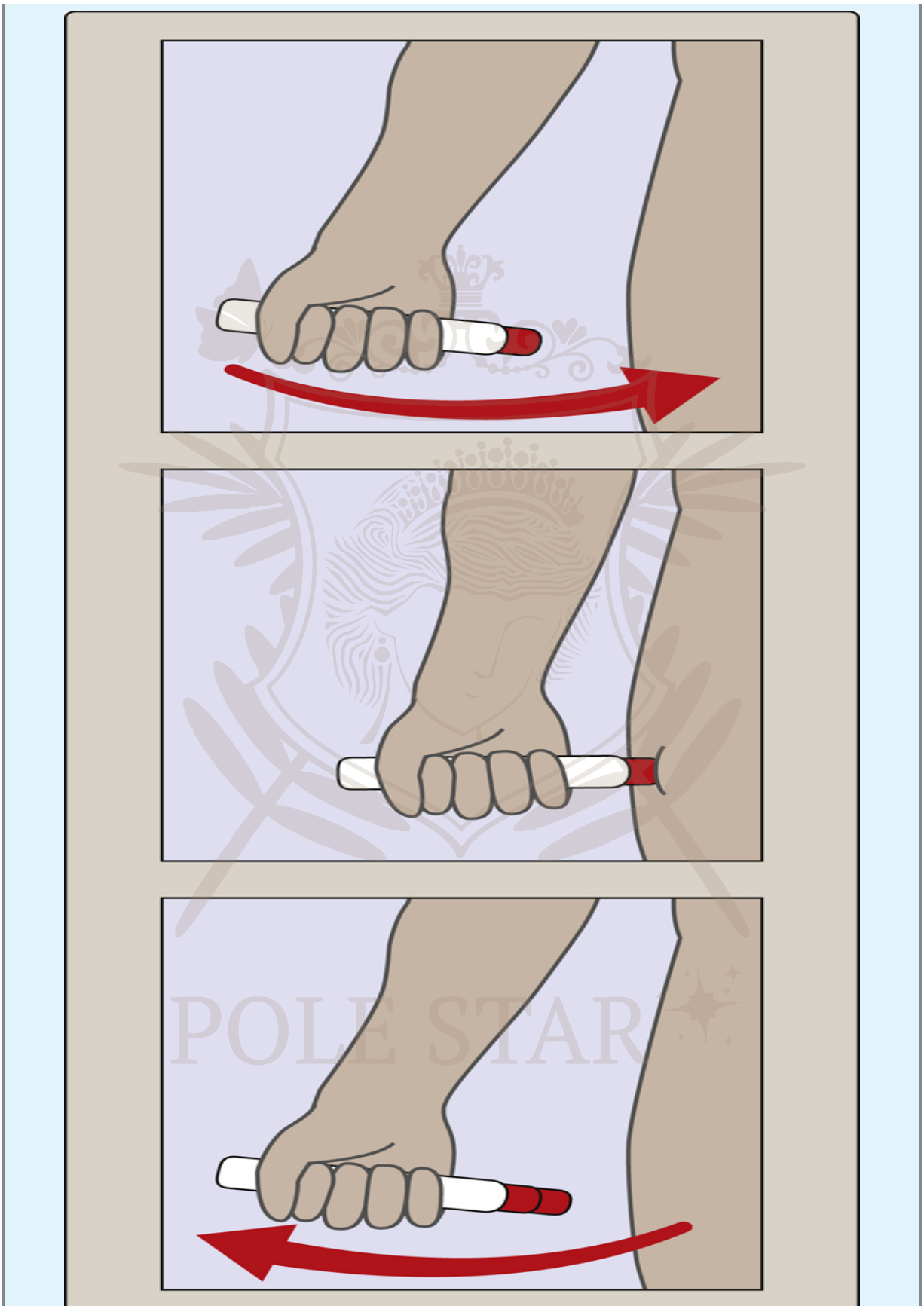

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B. Norepinephrine

Because *norepinephrine* [nor-ep-ih-NEF-rin] is the neurotransmitter in the adrenergic neurons, it should, theoretically, stimulate all types of adrenergic receptors. However, when administered in therapeutic doses, the α-adrenergic receptor is most affected.

1. Cardiovascular actions

a. Vasoconstriction: *Norepinephrine* causes a rise in peripheral resistance due to intense vasoconstriction of most vascular beds, including the kidney (α_1 effect). Both systolic and diastolic blood pressures increase (Figure 6.11). [Note: *Norepinephrine* causes greater vasoconstriction than *epinephrine*, because it does not induce compensatory vasodilation via β_2 receptors on blood vessels supplying skeletal muscles. The weak β_2 activity of *norepinephrine* also explains why it is not useful in the treatment of bronchospasm or anaphylaxis.]

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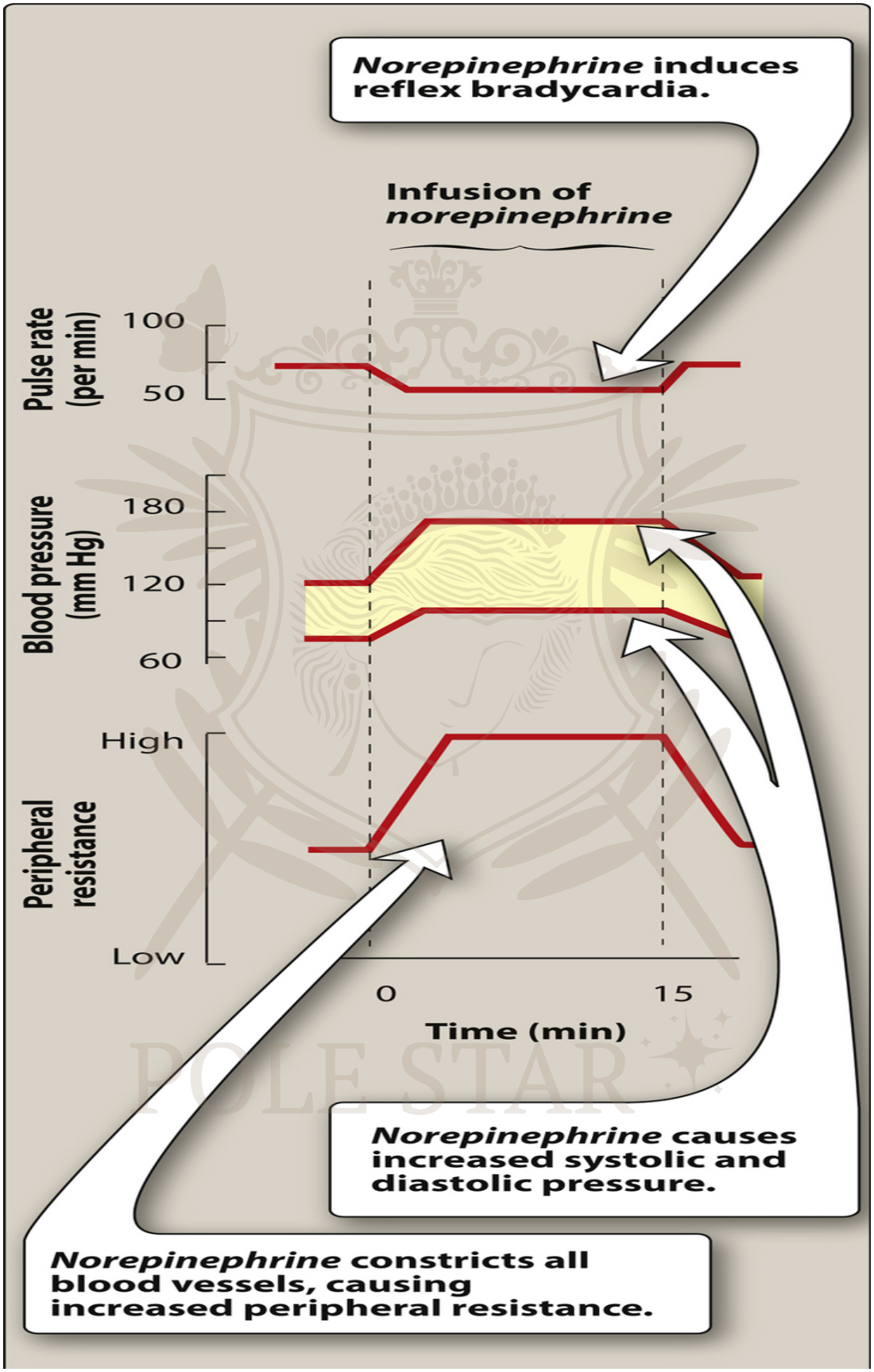
Norepinephrine induces reflex bradycardia.
Infusion of *norepinephrine*
Pulse rate (per min)
100
50
Blood pressure (mm Hg)
180
120
60
Peripheral resistance
High
Low
0
15
Time (min)
Norepinephrine causes increased systolic and diastolic pressure.
Norepinephrine constricts all blood vessels, causing increased peripheral resistance.

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Figure 6.11 Cardiovascular effects of intravenous infusion of *norepinephrine*.Modified from M. J.Allwood , A. F.Cobbold , and J.Ginsburg . Peripheral vascular effects of noradrenaline, isopropylnoradrenaline and dopamine. *Br. Med. Bull*. 19: 132 (1963).

b. Baroreceptor reflex: *Norepinephrine* increases blood pressure, and this stimulates the baroreceptors, inducing a rise in vagal activity. The increased vagal activity produces a reflex bradycardia (Figure 6.11), which is sufficient to counteract the local actions of *norepinephrine* on the heart, although the reflex compensation does not affect the positive inotropic effects of the drug. When *atropine*, which blocks the transmission of vagal effects, is given before *norepinephrine*, stimulation of the heart by *norepinephrine* is evident as tachycardia.

2.Therapeutic uses: *Norepinephrine* is used to treat shock (for example, septic shock), because it increases vascular resistance and, therefore, increases blood pressure. It has no other clinically significant uses.

3.Pharmacokinetics: *Norepinephrine* is given IV for rapid onset of action. The duration of action is 1 to 2 minutes, following the end of the infusion. Thus, it is usually administered as a continuous IV infusion in the management of shock. It is rapidly metabolized by MAO and COMT, and inactive metabolites are excreted in the urine.

4.Adverse effects: The adverse effects are similar to those of *epinephrine.* In addition, *norepinephrine* is a potent vasoconstrictor and may cause blanching and sloughing of skin along an injected vein. If extravasation (leakage of drug from the vessel into tissues surrounding the injection site) occurs, it can cause tissue necrosis. *Norepinephrine* should not be administered in peripheral veins, if possible. Impaired

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circulation from *norepinephrine* may be treated with the α receptor antagonist *phentolamine.* Alternatives to *phentolamine* include intradermal *terbutaline* and topical *nitroglycerin*.

C. Dopamine

Dopamine [DOE-pa-meen], the immediate metabolic precursor of *norepinephrine*, occurs naturally in the CNS in the basal ganglia, where it functions as a neurotransmitter, as well as in the adrenal medulla. *Dopamine* can activate α- and β-adrenergic receptors. For example, at higher doses, it causes vasoconstriction by activating α_1 receptors, whereas at lower doses, it stimulates β_1 cardiac receptors. In addition, D_1 and D_2 dopaminergic receptors, distinct from the α- and β-adrenergic receptors, occur in the peripheral mesenteric and renal vascular beds, where binding of *dopamine* produces vasodilation. D_2 receptors are also found on presynaptic adrenergic neurons, where their activation interferes with *norepinephrine* release.

1.Actions

a. Cardiovascular: *Dopamine* exerts a stimulatory effect on the β_1 receptors of the heart, having both positive inotropic and chronotropic effects (Figure 6.12). At very high doses, *dopamine* activates α_1 receptors on the vasculature, resulting in vasoconstriction.

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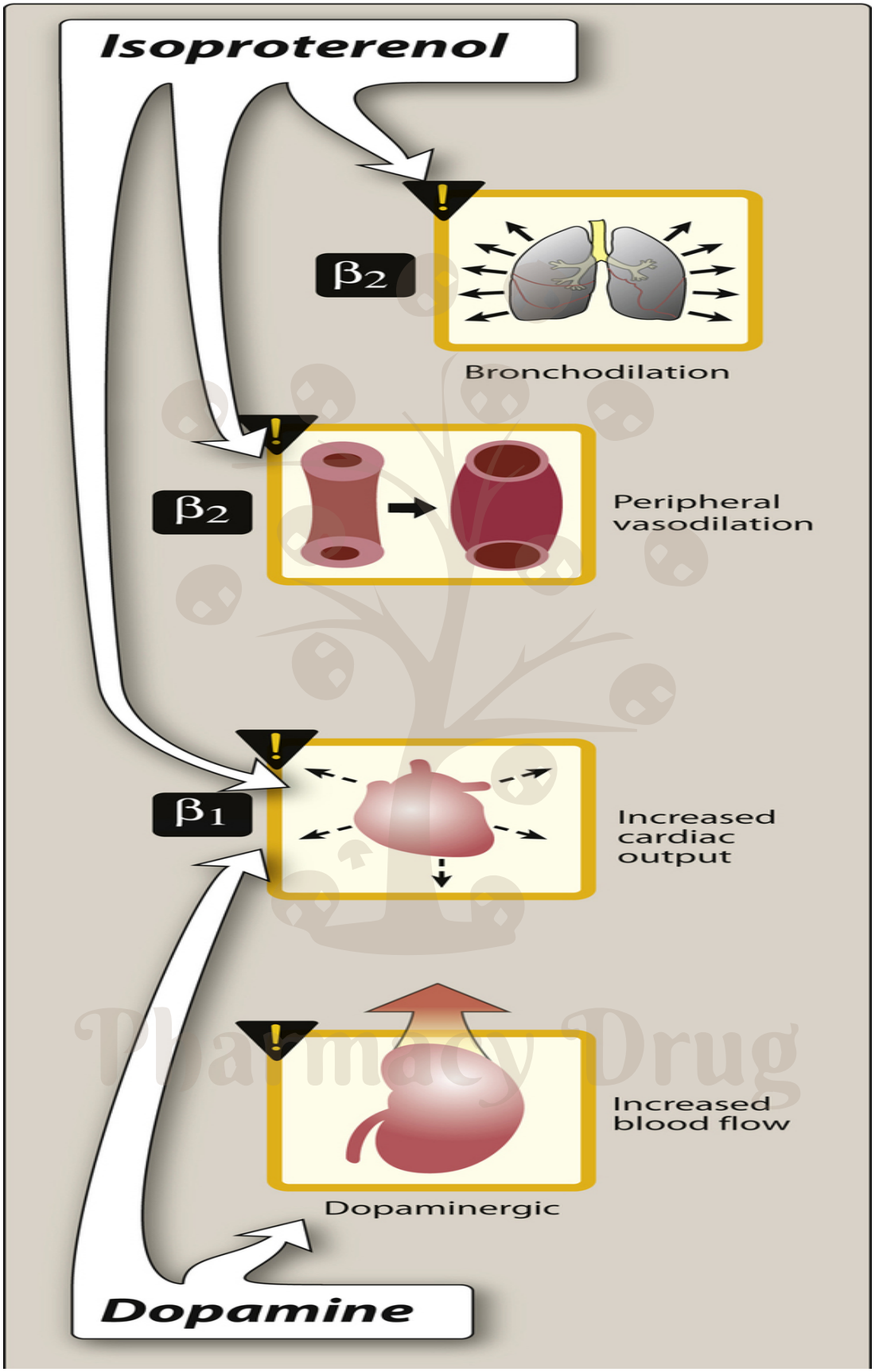

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Figure 6.12 Clinically important actions of *dopamine* and *isoproterenol*.

b. Renal and visceral: *Dopamine* dilates renal and splanchnic arterioles by activating dopaminergic receptors, thereby increasing blood flow to the kidneys and other viscera (Figure 6.12). These receptors are not affected by α- or β-blocking drugs, and in the past, low-dose ("renal-dose") *dopamine* was often used in the prevention or treatment of acute renal failure. However, more recent data suggest there is limited clinical utility in the renal protective effects of *dopamine*.

2. Therapeutic uses: *Dopamine* can be used for cardiogenic and septic shock and is given by continuous IV infusion. It raises blood pressure by stimulating the β_1 receptors on the heart to increase cardiac output and α_1 receptors on blood vessels to increase total peripheral resistance. It enhances perfusion to the kidney and splanchnic areas, as described above. Increased blood flow to the kidney enhances the glomerular filtration rate and causes diuresis. By contrast, *norepinephrine* can diminish blood supply to the kidney and may reduce renal function. *Dopamine* is also used to treat hypotension, severe heart failure, and bradycardia unresponsive to other treatments.

3. Adverse effects: An overdose of *dopamine* produces the same effects as sympathetic stimulation. *Dopamine* is rapidly metabolized by MAO or COMT, and its adverse effects (nausea, hypertension, and arrhythmias) are, therefore, short-lived.

D. Phenylephrine

Phenylephrine [fen-ill-EF-reen] is a direct-acting, synthetic adrenergic drug that binds primarily to α_1 receptors.

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Phenylephrine is a vasoconstrictor that raises both systolic and diastolic blood pressures. It has no effect on the heart itself but, rather, induces reflex bradycardia when given parenterally. The drug is used to treat hypotension in hospitalized or surgical patients (especially those with a rapid heart rate). Large doses can cause hypertensive headache and cardiac irregularities. *Phenylephrine* acts as a nasal decongestant when applied topically or taken orally. Although data suggest it may not be as effective, *phenylephrine* has replaced *pseudoephedrine* in many oral decongestants, since *pseudoephedrine* has been misused to synthesize *methamphetamine. Phenylephrine* is also used in ophthalmic solutions for mydriasis.

E. Naphazoline, oxymetazoline, and tetrahydrozoline

Naphazoline [naf-AZ-oh-leen], *oxymetazoline* [oks-i-met-AZ-oh-leen], and *tetrahydrozoline* [tet-ra-hye-DROZ-a-leen] are direct-acting synthetic adrenergic agonists that stimulate both α_1- and α_2-adrenergic receptors. These agents find clinical use in their ability to cause local vasoconstriction when applied topically (α_1 agonist effect). *Naphazoline*, *oxymetazoline*, and *tetrahydrozoline* are found in many over-the-counter nasal spray decongestants, as well as in ophthalmic drops for the relief of redness of the eyes. These agents directly stimulate α receptors on blood vessels supplying the nasal mucosa and conjunctiva, thereby producing vasoconstriction and decongestion. [Note: *Oxymetazoline* is also used as a topical cream to reduce skin redness associated with rosacea (see Chapter 45).] *Oxymetazoline* is absorbed in the systemic circulation regardless of the route of administration and may produce nervousness, headaches, and trouble sleeping. It is unknown if *naphazoline* or *tetrahydrozoline* reach significant levels in the systemic circulation. Local irritation and sneezing may occur with intranasal administration of these drugs. Use for greater than 3 days is not recommended, as rebound congestion and dependence may occur.

F. Midodrine

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Midodrine [MI-doe-dreen], a prodrug, is metabolized to the pharmacologically active desglymidodrine. It is a selective α_1 agonist, which acts in the periphery to increase arterial and venous tone. *Midodrine* is indicated for the treatment of orthostatic hypotension. The drug should be given three times daily, with doses at 3- or 4-hour intervals. To avoid supine hypertension, doses within 4 hours of bedtime are not recommended.

G. Clonidine

Clonidine [KLOE-ni-deen] is an α_2 agonist used for the treatment of hypertension. *Clonidine* acts centrally on presynaptic α_2 receptors to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery. It can also be used to minimize symptoms of withdrawal from opiates, tobacco smoking, and benzodiazepines. Both *clonidine* and the α_2 agonist *guanfacine* [GWAHN-fa-seen] may be used in the management of attention deficit hyperactivity disorder (see Chapter 22). The most common side effects of *clonidine* are lethargy, sedation, constipation, and xerostomia. Abrupt discontinuation must be avoided to prevent rebound hypertension. *Clonidine* and another α_2 agonist *methyldopa* are discussed with antihypertensives in Chapter 8. [Note: Ophthalmic preparations of the α_2 agonists *apraclonidine* and *brimonidine* are used in the treatment of glaucoma or ocular hypertension. Topical *brimonidine* is also used in the treatment of rosacea (see Chapter 45).]

H. Dobutamine

Dobutamine [doe-BYOO-ta-meen] is a synthetic, direct-acting catecholamine that is primarily a β_1 receptor agonist with minor β_2 and α_1 effects. It increases heart rate and cardiac output with few vascular effects. *Dobutamine* is used to increase cardiac output in acute heart failure (see Chapter 10), as well as for inotropic support after cardiac surgery. The drug increases cardiac output and does not elevate oxygen demands of the myocardium as much as other sympathomimetic drugs. *Dobutamine* should be

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used with caution in atrial fibrillation, because it increases atrioventricular conduction. Other adverse effects are similar to *epinephrine.* Tolerance may develop with prolonged use.

I. Isoproterenol

Isoproterenol [eye-soe-proe-TER-e-nole] is a direct-acting synthetic catecholamine that stimulates both β_1- and β_2-adrenergic receptors. Its nonselectivity is a disadvantage and the reason why it is rarely used therapeutically. Its action on α receptors is insignificant. *Isoproterenol* produces intense stimulation of the heart (β_1 effect), increasing heart rate, contractility, and cardiac output (Figure 6.12). It is as active as *epinephrine* in this action. *Isoproterenol* also dilates the arterioles of skeletal muscle (β_2 effect), resulting in decreased peripheral resistance. Because of its cardiac stimulatory action, it may increase systolic blood pressure slightly, but it greatly reduces mean arterial and diastolic blood pressures (Figure 6.13). *Isoproterenol* is also a potent bronchodilator (β_2 effect). The adverse effects of *isoproterenol* are similar to the β receptor–related side effects of *epinephrine*.

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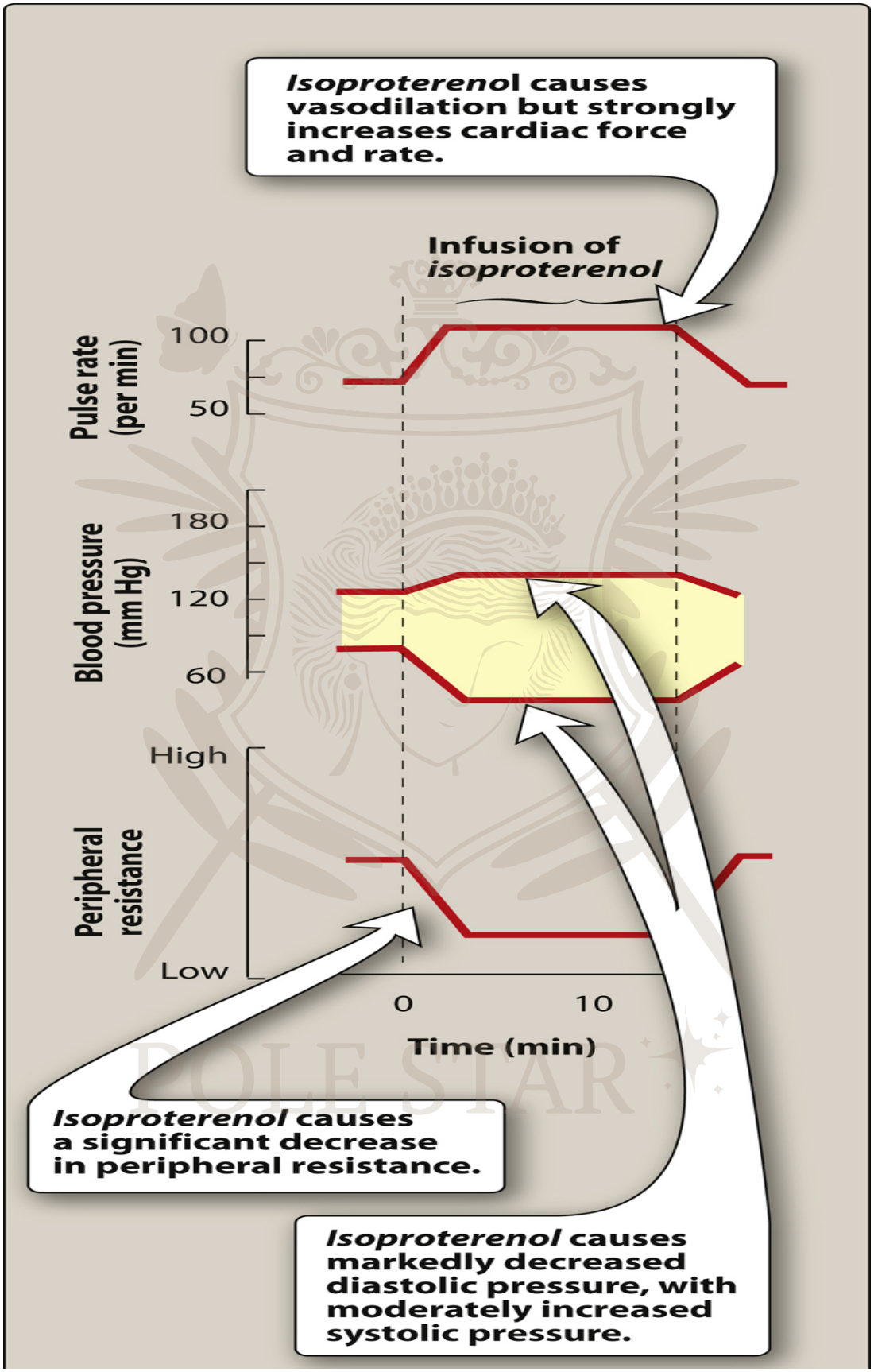
Isoproterenol causes vasodilation but strongly increases cardiac force and rate.
Infusion of *isoproterenol*
Pulse rate (per min)
100
50
Blood pressure (mm Hg)
180
120
60
Peripheral resistance
High
Low
0
10
Time (min)
Isoproterenol causes a significant decrease in peripheral resistance.
Isoproterenol causes markedly decreased diastolic pressure, with moderately increased systolic pressure.

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Figure 6.13 Cardiovascular effects of intravenous infusion of *isoproterenol*.

J. Albuterol, levalbuterol, metaproterenol, and terbutaline

Albuterol [al-BYOO-ter-ol], *levalbuterol* [leh-val-BYOO-ter-ol], *metaproterenol* [MET-a-proe-TER-e-nol], and *terbutaline* [ter-BYOO-te-leen] are short-acting β_2 agonists (SABAs) used primarily as bronchodilators, usually administered by metered-dose inhalers (Figure 6.14). *Albuterol* and its R-isomer *levalbuterol* are the SABAs of choice for the management of acute bronchospasm, because these agents are more selective for β_2 receptors than *metaproterenol.* Inhaled *terbutaline* is no longer available in the United States but is still used in other countries. Injectable *terbutaline* is used for the reversal of acute bronchospasm and off-label as a uterine relaxant to suppress premature labor (use for this indication should not exceed 48-72 hours). One of the most common side effects of these agents is tremor, but patients tend to develop tolerance to this effect. Other side effects include restlessness, apprehension, and anxiety. When these drugs are administered orally, they may cause tachycardia or arrhythmia (due to β_1 receptor activation), especially in patients with underlying cardiac disease. Monoamine oxidase inhibitors (MAOIs) also increase the risk of adverse cardiovascular effects, and concomitant use should be avoided. Use of nonselective beta antagonists can diminish or counteract the bronchodilatory effects of SABAs.

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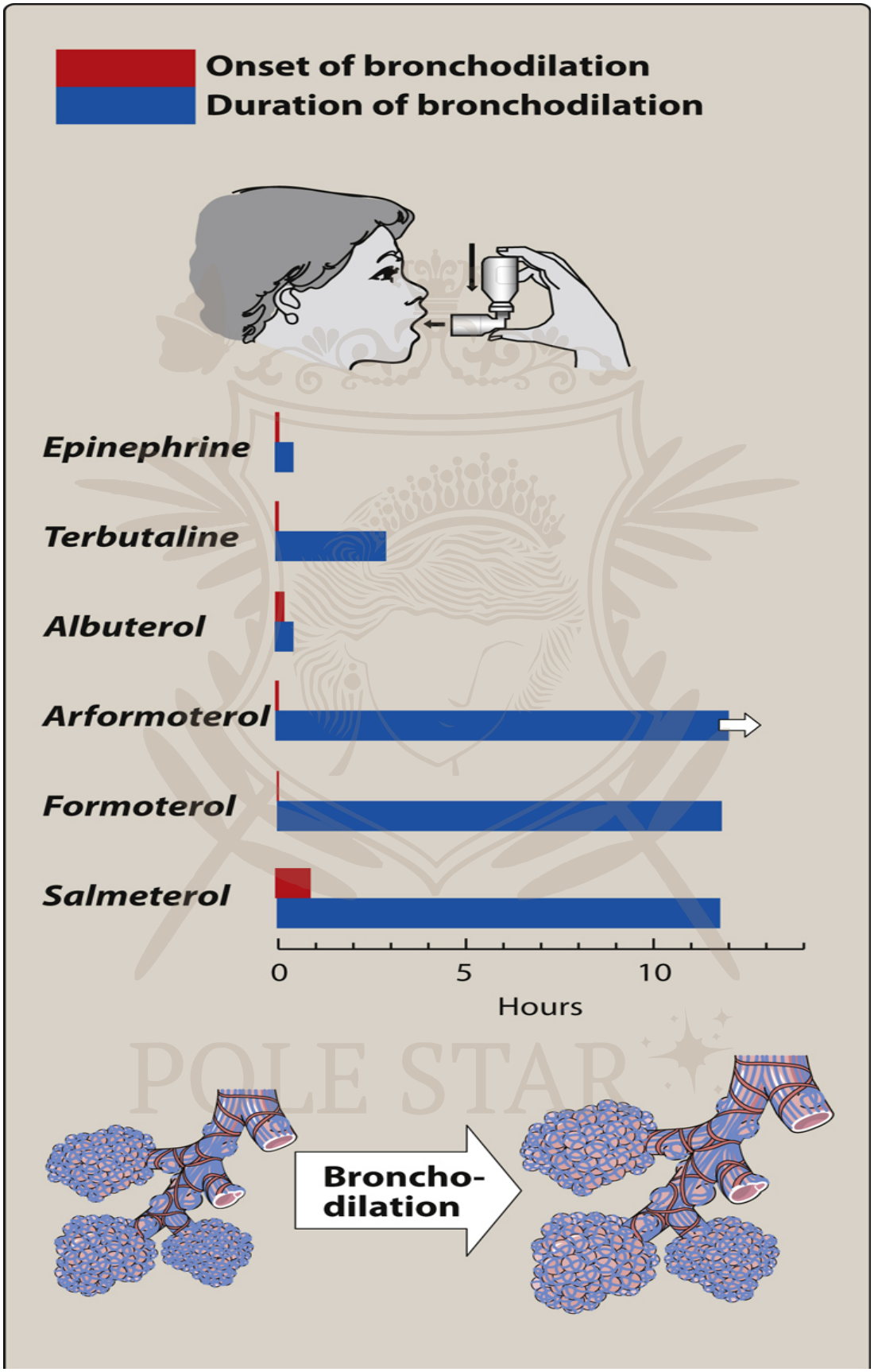
Onset of bronchodilation
Duration of bronchodilation
Epinephrine
Terbutaline
Albuterol
Arformoterol
Formoterol
Salmeterol
0
5
10
Hours
Broncho-
dilation

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Figure 6.14 Onset and duration of bronchodilation effects of inhaled adrenergic agonists.

K. Formoterol, indacaterol, olodaterol, and salmeterol

Formoterol [for-MOH-ter-ol], *arformoterol* (the [R,R]-enantiomer of *formoterol*), *indacaterol* [IN-da-KA-ter-ol], *olodaterol* [OH-loe-DAT-er-ol], and *salmeterol* [sal-ME-ter-ol] are long-acting β_2 selective agonists (LABAs) used for the management of respiratory disorders such as asthma and chronic obstructive pulmonary disease (see Chapter 41). A single dose by a metered-dose inhalation device, such as a dry powder inhaler, provides sustained bronchodilation over 12 hours, compared with less than 3 hours for *albuterol.* Unlike *formoterol*, however, *salmeterol* has a somewhat delayed onset of action (Figure 6.14). LABAs are not recommended as monotherapy for the treatment of asthma, because they have been shown to increase the risk of asthma-related deaths; however, these agents are highly efficacious when combined with an asthma controller medication such as an inhaled corticosteroid.

L. Mirabegron and vibegron

Mirabegron [mir-a-BEG-ron] and *vibegron* [vye-BEG-ron] are β_3 agonists that relax the detrusor smooth muscle and increase bladder capacity. These agents are used for patients with overactive bladder. *Mirabegron* may increase blood pressure and should not be used in patients with uncontrolled hypertension. Both drugs may increase the levels of *digoxin* by inhibiting p-glycoprotein-mediated elimination, and *mirabegron* inhibits the CYP2D6 isozyme, which may enhance the effects of other medications metabolized by this pathway (for example, *metoprolol*). *Vibegron* has minimal interaction with the CYP450 enzyme system; hence, the potential for drug interactions is less when compared with *mirabegron*.

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Clinical Application 6.2: β_3 Agonists in the Treatment of Overactive Bladder

Overactive bladder (OAB) is a condition characterized by bothersome urinary symptoms. Urinary urgency (defined as a sudden, strong need to pass urine that is difficult to delay) is considered a hallmark symptom. Other symptoms may include urinary frequency, nocturia (the need to wake to urinate), and, in some cases, urge urinary incontinence. Patients are diagnosed with OAB through self-report of urinary symptoms and exclusion of other disorders. Initial treatment for OAB includes behavioral modifications, such as fluid management, pelvic floor muscle exercises, and bladder control strategies. Pharmacotherapy may be considered for patients who do not obtain satisfactory response to behavioral modifications. β_3 Agonists, such as *mirabegron* and *vibegron,* help to relieve the symptoms of OAB by relaxing the detrusor muscle. Relaxation of the detrusor muscle increases the storage capacity of the bladder and reduces symptoms of urgency, frequency, and incontinence. Either β_3 agonists or the antimuscarinic drugs (see Chapter 5) are considered first-line agents for the management of OAB. Combination therapy with a β_3 agonist and an antimuscarinic drug may be used in patients who fail to respond to therapy with a single agent.

V. INDIRECT-ACTING ADRENERGIC AGONISTS

Indirect-acting adrenergic agonists cause the release, inhibit the reuptake, or inhibit the degradation of epinephrine or norepinephrine (Figure 6.8). They potentiate the effects of epinephrine or norepinephrine produced endogenously but do not directly bind to or affect postsynaptic receptors.

A. Amphetamine

The marked central stimulatory action of *amphetamine* [am-FET-a-meen] is often mistaken by drug abusers as its only action. However, the drug can also increase blood pressure significantly by α_1 agonist action on the vasculature, as well as β_1 stimulatory effects on the heart. Its actions are mediated primarily through an

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increase in nonvesicular release of catecholamines such as dopamine and norepinephrine from nerve terminals. This mechanism is complemented by inhibition of reuptake of these catecholamines and also by inhibition of monoamine oxidase (MAO). Thus, *amphetamine* is an indirect-acting adrenergic drug. The actions and therapeutic uses of *amphetamine* and its derivatives are discussed with CNS stimulants (see Chapter 22).

B. Tyramine

Tyramine [TIE-ra-meen] is not a clinically useful drug, but it is important because it is found in fermented foods, such as aged cheese and Chianti wine. It is a normal by-product of tyrosine metabolism. Normally, it is oxidized by MAO in the gastrointestinal tract, but if the patient is taking MAOIs, it can precipitate serious vasopressor episodes. Like *amphetamines*, *tyramine* can enter the nerve terminal and displace stored norepinephrine. The released catecholamine then acts on adrenoceptors.

C. Cocaine

Cocaine [koe-KANE] is unique among local anesthetics in having the ability to block the sodium–chloride (Na^+/Cl^-)–dependent norepinephrine transporter required for reuptake of norepinephrine into the adrenergic neuron. Consequently, norepinephrine accumulates in the synaptic space, resulting in enhanced sympathetic activity and potentiation of the actions of epinephrine and norepinephrine. Therefore, small doses of the catecholamines produce greatly magnified effects in an individual taking *cocaine.* In addition, the duration of action of epinephrine and norepinephrine is increased. Like *amphetamines*, it can increase blood pressure by indirect α_1 agonist actions and β stimulatory effects. *Cocaine* as a drug of abuse is discussed in Chapter 47.

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VI. MIXED-ACTION ADRENERGIC AGONISTS

Ephedrine [eh-FED-rin] and *pseudoephedrine* [soo-doe-eh-FED-rin] are mixed-action adrenergic agents. They not only enhance release of stored norepinephrine from nerve endings (Figure 6.8) but also directly stimulate both α and β receptors. Thus, a wide variety of adrenergic actions ensue that are similar to those of *epinephrine*, although less potent. *Ephedrine* and *pseudoephedrine* are not catecholamines and are poor substrates for COMT and MAO. Therefore, these drugs have a long duration of action. *Ephedrine* and *pseudoephedrine* have excellent absorption after oral administration and penetrate the CNS, but *pseudoephedrine* has fewer CNS effects. *Ephedrine* is eliminated largely unchanged in urine, and *pseudoephedrine* undergoes incomplete hepatic metabolism before elimination in urine. *Ephedrine* raises systolic and diastolic blood pressures by vasoconstriction and cardiac stimulation and is indicated in anesthesia-induced hypotension. *Ephedrine* produces bronchodilation, but it is less potent and slower acting than *epinephrine* or *isoproterenol.* It was previously used to prevent asthma attacks but has been replaced by more effective medications. *Ephedrine* produces a mild stimulation of the CNS. This increases alertness, decreases fatigue, and prevents sleep. It also improves athletic performance. [Note: The clinical use of *ephedrine* is declining because of the availability of better, more potent agents that cause fewer adverse effects. *Ephedrine*-containing herbal supplements (mainly ephedra-containing products) have been banned by the US Food and Drug Administration because of life-threatening cardiovascular reactions.] Oral *pseudoephedrine* is primarily used to treat nasal and sinus congestion. *Pseudoephedrine* has been illegally used to produce *methamphetamine.* Therefore, products containing *pseudoephedrine* have certain restrictions and must be kept behind the sales counter in the United States and several other countries. Important characteristics of the adrenergic agonists are summarized in Figures 6.15 - 6.17.

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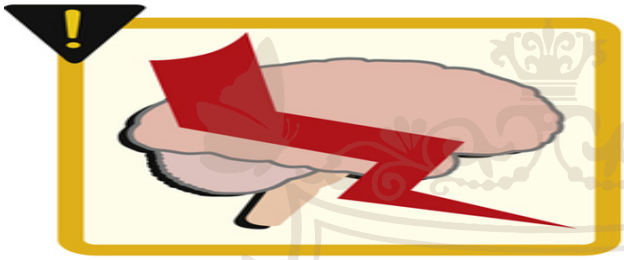
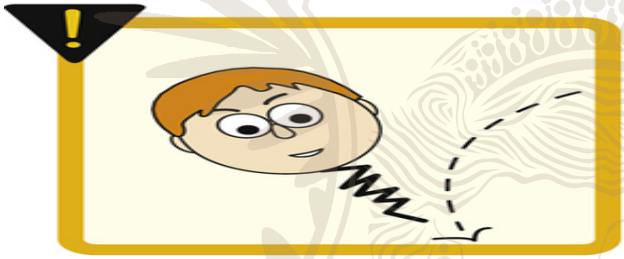
Arrhythmias



Headache



Hyperactivity

Insomnia

Nausea

Tremors

POLE STAR

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Figure 6.15 Some adverse effects observed with adrenergic agonists.

TISSUE	RECEPTOR TYPE	ACTION	OPPOSING ACTIONS
Heart			
• Sinus and AV	β_1	↑ Automaticity	Cholinergic receptors
• Conduction pathway	β_1	↑ Conduction velocity, automaticity	Cholinergic receptors
• Myofibrils	β_1	↑ Contractility, automaticity	
Vascular smooth muscle	β_2	Vasodilation	α-Adrenergic receptors
Bronchial smooth muscle	β_2	Bronchodilation	Cholinergic receptors
Kidneys	β_1	↑ Renin release	α_1-Adrenergic receptors
Liver	β_2, α_1	↑ Glycogenolysis and gluconeogenesis	—
Skeletal muscle	β_2	↑ Increased contractility Potassium uptake; glycogenolysis Dilates arteries to skeletal muscle Tremor	—
Eye-ciliary muscle	β_2	Relaxation	Cholinergic receptors
GI tract	β_2	↓ Motility	Cholinergic receptors
Gallbladder	β_2	Relaxation	Cholinergic receptors
Urinary bladder detrusor muscle	β_2, β_3	Relaxation	Cholinergic receptors
Uterus	β_2	Relaxation	Oxytocin
Adipose tissue	β_3	↑ Lipolysis	α_2-Adrenergic receptors

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Figure 6.16 Summary of β-adrenergic receptors.AV = atrioventricular; GI = gastrointestinal.

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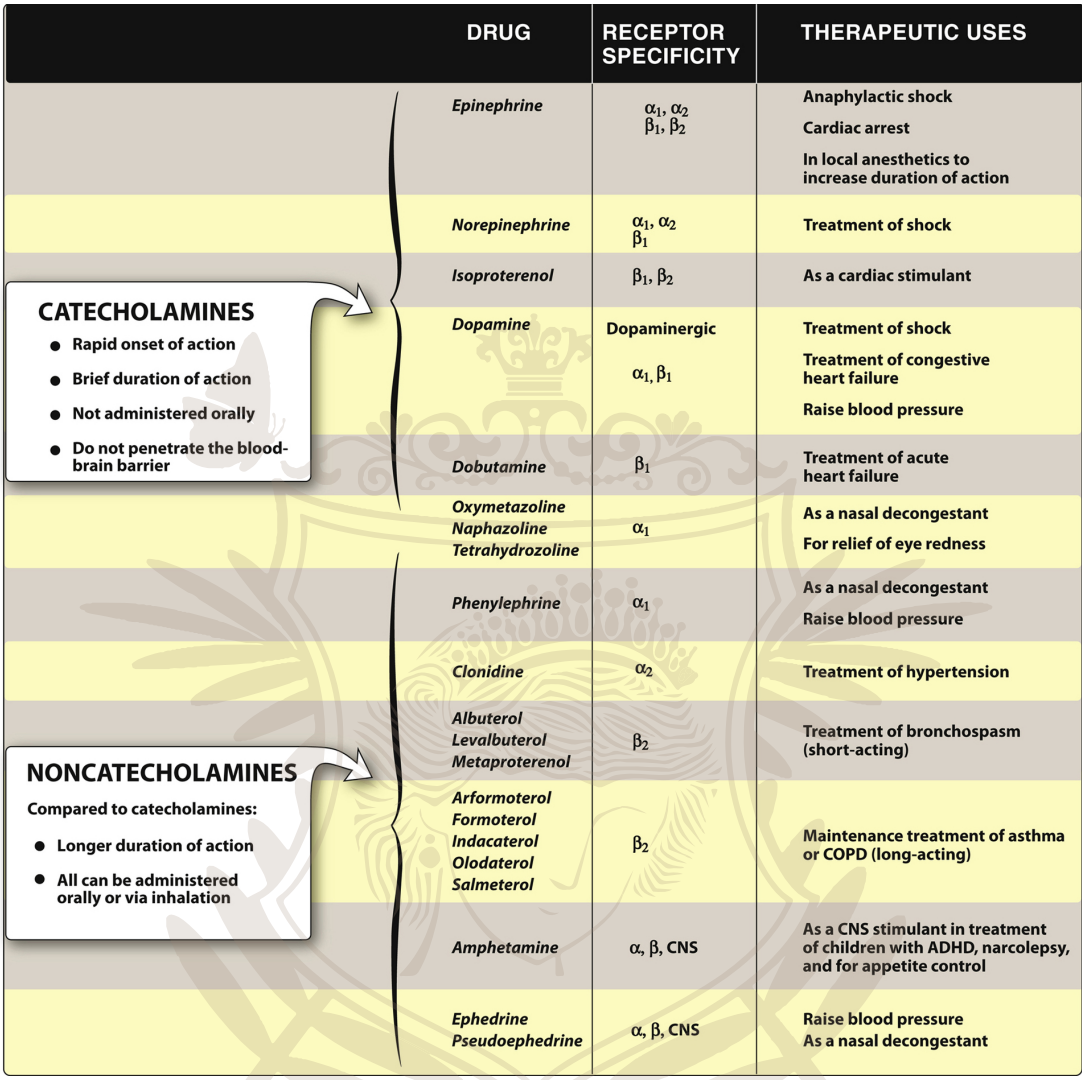

Figure 6.17 Summary of the therapeutic uses of adrenergic agonists.ADHD = attention deficit hyperactivity disorder; CNS = central nervous system; COPD = chronic obstructive pulmonary disease.

POLE STAR

Chapter Summary

- There are three classes of adrenergic agonists—direct-acting, indirect-acting, and mixed-action agonists.
- Direct-acting agonists act by directly stimulating α and/or β receptors.
- α_1 Agonists such as *phenylephrine* cause vasoconstriction by activating α_1 receptors and are mainly used in the treatment of nasal and sinus congestion.

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- α_2 Agonists such as *clonidine* activate presynaptic α_2 receptors causing feedback inhibition of norepinephrine release. These agents are mainly used in the treatment of hypertension.
- β_1 Agonists such as *dobutamine* activate β_1 receptors in the heart causing increased heart rate, contractility, and a subsequent increase in cardiac output. These agents are mainly used in the treatment of acute heart failure.
- β_2 Agonists such as *albuterol* exert their clinical effect by activating β_2 receptors in the bronchioles of the lungs, causing bronchodilation, and are used mainly in the treatment of asthma and chronic obstructive pulmonary disease.
- Indirect-acting adrenergic agonists work by blocking the reuptake of norepinephrine (for example, *cocaine* and *amphetamine*) and also by increasing its release or inhibiting its breakdown (for example, *amphetamine*). These agents do not directly affect postsynaptic adrenergic receptors.
- Mixed-action adrenergic agonists, such as *ephedrine* and *pseudoephedrine*, both enhance the release of norepinephrine and directly stimulate α and β adrenoceptors. *Pseudoephedrine* is mainly used in the treatment of nasal and sinus congestion.

STUDY QUESTIONS

Choose the ONE best answer.

6.1 Which of the following is the primary neurotransmitter released from postganglionic sympathetic neurons that innervate cardiac muscles?

A. Norepinephrine
B. Epinephrine
C. Dopamine
D. Acetylcholine

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Correct answer = A. Norepinephrine is the major neurotransmitter released from postganglionic sympathetic nerve terminals in cardiac tissues and vascular smooth muscles. Epinephrine is mainly released from the adrenal glands, and dopamine is released by postganglionic sympathetic neurons in the renal blood

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vessels. Acetylcholine is released by postganglionic parasympathetic neurons in the effector smooth muscles.

6.2 Which of the following adrenergic drugs is used in the treatment of overactive bladder?

A. Epinephrine
B. Dobutamine
C. Phenylephrine
D. Mirabegron

Correct answer = D. Detrusor muscles in the urinary bladder wall have β_3 receptors. Stimulation of these receptors relaxes the urinary bladder wall and relieves symptoms of overactive bladder. Mirabegron is a β_3 agonist and therefore used in treating overactive bladder. None of the other drugs listed have β_3 agonist activity.

6.3 Which of the following statements is correct regarding responses mediated by adrenergic receptors?

A. Stimulation of α_1 receptors increases blood pressure.
B. Stimulation of sympathetic presynaptic α_2 receptors increases norepinephrine release.
C. Stimulation of β_2 receptors increases heart rate (tachycardia).
D. Stimulation of β_2 receptors causes bronchoconstriction.

Correct answer = A. Stimulation of α_1 receptors, mostly found in the blood vessels, causes vasoconstriction and an increase in blood pressure. Stimulation of α_2 receptors on the sympathetic presynaptic terminal reduces the release of norepinephrine. β_2 Receptors are not found in the heart, so activation of β_2 receptors does not affect heart rate. Stimulation of β_2 receptors found in the bronchial tissues causes bronchodilation, not bronchoconstriction.

6.4 An asthma patient was given a nonselective β agonist to relieve bronchoconstriction. Which adverse effect would you

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expect in this patient?

A. Bradycardia
B. Tachycardia
C. Hypotension (reduction in blood pressure)
D. Worsening bronchoconstriction

Correct answer = B. A nonselective β agonist activates both β_1 and β_2 receptors. β_1 Activation causes an increase in heart rate (tachycardia), contractility, and subsequent increase in blood pressure. It relieves bronchoconstriction because of the β_2 receptor activation.

6.5 A 12-year-old boy with peanut allergy is brought to the emergency room after accidental consumption of peanuts. He is in anaphylactic shock. Which of the following drugs is most appropriate to treat this patient?

A. Norepinephrine
B. Phenylephrine
C. Dobutamine
D. Epinephrine

Correct answer = D. Norepinephrine has more α agonistic effects and activates mainly α_1, α_2, and β_1 receptors. Epinephrine has more β agonistic effects and activates mainly α_1, α_2, β_1, and β_2 receptors. Phenylephrine has predominantly α effects and activates mainly α_1 receptors. Dobutamine mainly activates β_1 receptors and has no significant effects on β_2 receptors. Thus, epinephrine is the drug of choice in anaphylactic shock that can both stimulate the heart (β_1 activation) and dilate bronchioles (β_2 activation).

6.6 An elderly patient is brought to the emergency room with a blood pressure of 76/60 mm Hg, tachycardia, and low cardiac output. He is diagnosed with acute heart failure. Which of the following drugs is most appropriate to improve his cardiac function?

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A. Epinephrine
B. Clonidine
C. Dobutamine
D. Isoproterenol

Correct answer = C. Among the choices, the ideal drug to increase contractility in acute heart failure is dobutamine, since it is a selective β_1-adrenergic agonist. Clonidine is an α_2 agonist used to treat hypertension (not hypotension). The other drugs are nonselective adrenergic agonists that could cause unwanted side effects.

6.7 Epinephrine is added to local anesthetic formulations used in dental procedures to extend their duration of action. Which of the following adrenergic receptors contribute to the increased duration of action of local anesthetics?

A. α_1
B. α_2
C. β_1
D. β_2

Correct answer = A. When injected into the tissues, epinephrine causes constriction of local vasculature by the activation of α_1 receptors. The constriction of vasculature reduces the removal of local anesthetic from the injected tissue and prolongs the local anesthetic effect. Activation of other adrenergic receptors does not lead to vasoconstriction.

6.8 Which of the following adrenergic agonists used in the treatment of asthma increases the risk of asthma-related deaths when used as a single agent?

A. Albuterol
B. Epinephrine
C. Ephedrine
D. Salmeterol

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Correct answer = D. Long-acting β agonists (LABAs) such as salmeterol have been shown to increase the risk of asthma-related deaths when used alone and have a boxed warning related to this. The combination of a LABA with an inhaled corticosteroid is a preferred regimen for moderate to severe asthma.

6.9 Which of the following adrenergic agents has restrictions on over-the-counter sales because of its potential use for the illegal synthesis of methamphetamine?

A. Naphazoline
B. Pseudoephedrine
C. Epinephrine
D. Tetrahydrozoline

Correct answer = B. Pseudoephedrine is a direct precursor in the synthesis of methamphetamine, owing to its stereochemical structural similarity to methamphetamine. The chemical structures of the other listed drugs do not lend themselves to the synthesis of methamphetamine.

6.10 A pharmaceutical company develops a new drug to treat the symptoms of chronic obstructive pulmonary disease. In preclinical studies, the drug caused bronchodilation but did not cause significant vasoconstriction, nor an increase in heart rate or contractility. Which of the following drugs does this new drug resemble?

A. Epinephrine
B. Arformoterol
C. Norepinephrine
D. Dobutamine

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Correct answer = B. Since the new drug causes bronchodilation and does not cause vasoconstriction or increase in heart rate and contractility, the drug is likely to have β_2 agonistic activity but not α_1 or β_1 agonistic activity, which is similar to arformoterol that is a selective β_2 agonist. Epinephrine, norepinephrine, and dobutamine cause an increase in blood pressure.

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7

Adrenergic Antagonists

Sandhya Jinesh, Rajan Radhakrishnan

I. OVERVIEW

The adrenergic antagonists (also called adrenergic blockers or sympatholytics) bind to adrenoceptors but do not trigger the usual receptor-mediated intracellular effects. These drugs act by either reversibly or irreversibly binding to the adrenoceptors, thus preventing activation by endogenous or exogenous agonists. Like the agonists, the adrenergic antagonists are classified according to their relative affinities for α or β receptors in the sympathetic nervous system. Numerous adrenergic antagonists have important roles in clinical medicine, primarily in treating diseases associated with the cardiovascular system. [Note: Antagonists that block dopamine receptors are most important in the central nervous system (CNS) and are, therefore, considered in that section.] The adrenergic antagonists discussed in this chapter are summarized in Figure 7.1.

POLE STAR

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α-BLOCKERS

Alfuzosin UROXATRAL
Doxazosin CARDURA
Phenoxybenzamine DIBENZYLINE
Phentolamine GENERIC ONLY
Prazosin MINIPRESS
Silodosin RAPAFLO
Tamsulosin FLOMAX
Terazosin GENERIC ONLY

β-BLOCKERS

Acebutolol GENERIC ONLY
Atenolol TENORMIN
Betaxolol BETOPTIC-S
Bisoprolol GENERIC ONLY
Carteolol GENERIC ONLY
Carvedilol COREG, COREG CR
Esmolol BREVIBLOC
Labetalol GENERIC ONLY
Levobunolol BETAGAN
Metoprolol LOPRESSOR, TOPROL-XL
Nadolol CORGARD
Nebivolol BYSTOLIC
Pindolol GENERIC ONLY
Propranolol INDERAL LA, INNOPRAN XL
Timolol BETIMOL, ISTALOL, TIMOPTIC

DRUGS AFFECTING NEUROTRANSMITTER UPTAKE OR RELEASE

Reserpine GENERIC ONLY

Pharmacy Drug

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Figure 7.1 Summary of blocking agents and drugs affecting neurotransmitter uptake or release.

II. A-ADRENERGIC BLOCKING AGENTS

α-Adrenergic blocking agents antagonize the subtype(s) of α-adrenergic receptors (α_1 or α_2), depending on the specificity of the agent for the receptor subtype(s). Drugs that block α_1-adrenoceptors significantly affect blood pressure. Because normal sympathetic control of the vasculature occurs in large part through agonist actions on α_1-adrenergic receptors, blockade of these receptors reduces the sympathetic tone of the blood vessels, resulting in decreased peripheral vascular resistance and a subsequent reduction in blood pressure. This decreased blood pressure induces reflex tachycardia. The magnitude of the response depends on the sympathetic tone of the individual when the agent is administered. Selective α_2-adrenergic blockers can theoretically increase the release of norepinephrine but have limited clinical utility.

A. Phenoxybenzamine

Phenoxybenzamine [fen-ox-ee-BEN-za-meen] is an irreversible (noncompetitive), nonselective blocker of α_1- and α_2-adrenergic receptors.

POLE STAR

1. Actions

a. Cardiovascular effects: The drug prevents α_1 receptor-mediated vasoconstriction of peripheral blood vessels caused by endogenous catecholamines, which leads to decreased peripheral resistance and resultant reflex tachycardia. However, by blocking presynaptic α_2

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receptors on the sympathetic nerve terminals in the heart, *phenoxybenzamine* causes an increase in the release of norepinephrine, which in turn increases heart rate and cardiac output (mediated by β_1 receptors). This may also lead to cardiac arrhythmias and anginal pain. For these reasons, *phenoxybenzamine* is not used as a maintenance therapy for the treatment of hypertension, although it is useful in the short-term management of some hypertensive crises.

b. Epinephrine reversal: All α-adrenergic blockers reverse the α agonist actions of *epinephrine.* For example, the vasoconstrictive action of *epinephrine* is interrupted, but vasodilation of other vascular beds caused by stimulation of β_2 receptors is not blocked. Therefore, in the presence of *phenoxybenzamine*, the systemic blood pressure decreases in response to *epinephrine* (Figure 7.2). [Note: The actions of *norepinephrine* are not reversed but are diminished because *norepinephrine* lacks significant β agonist action on the vasculature.] *Phenoxybenzamine* has no effect on the actions of *isoproterenol*, which is a pure β agonist (Figure 7.2).

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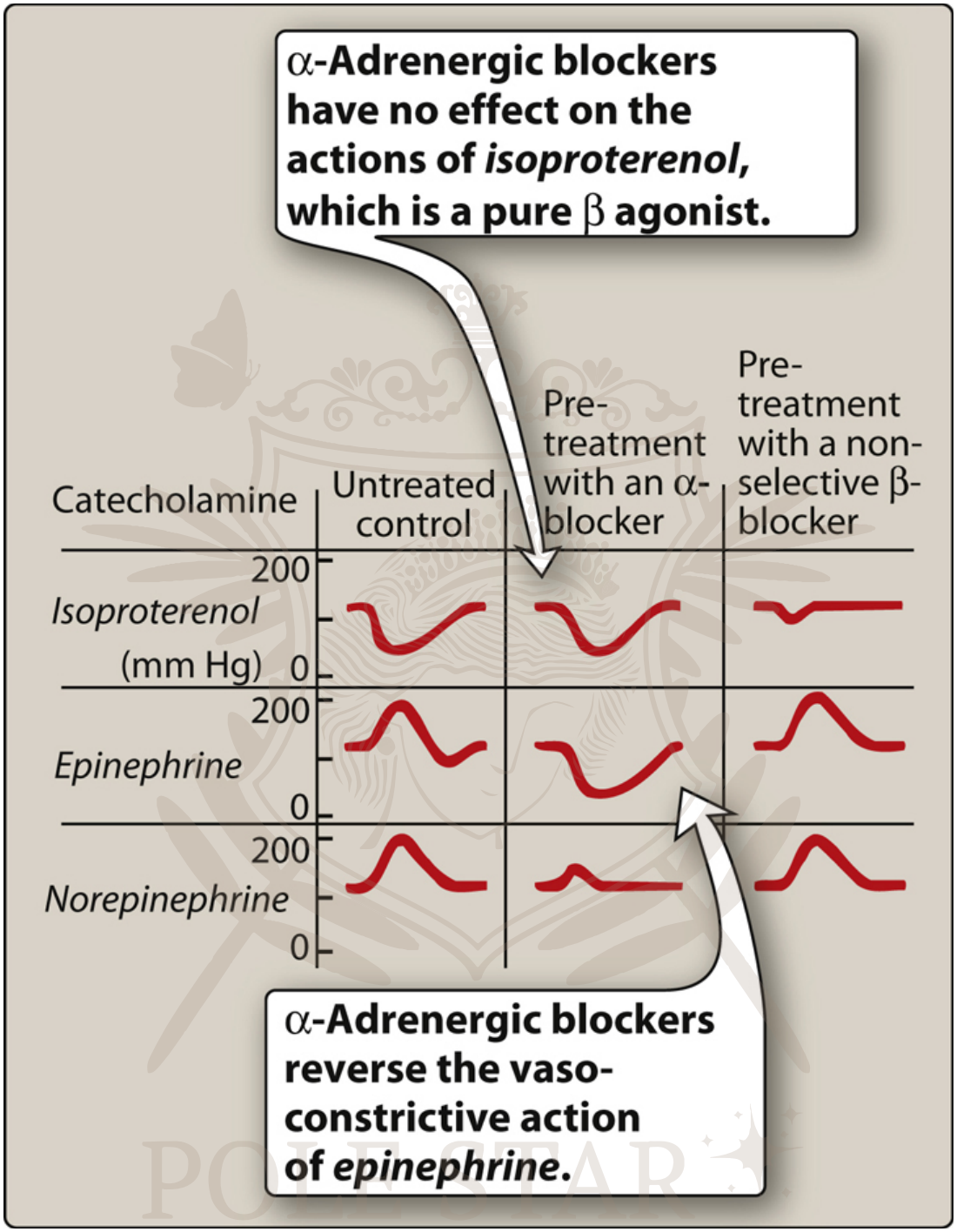

Figure 7.2 Summary of effects of adrenergic blockers on the changes in blood pressure induced by *isoproterenol*, *epinephrine*, and *norepinephrine*.

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2.Therapeutic uses: *Phenoxybenzamine* is indicated in the treatment of sweating and hypertension associated with pheochromocytoma, a catecholamine-secreting tumor in the adrenal medulla. Off-label uses include treatment of hypertensive crisis caused by sympathomimetic amines, urinary problems associated with neurogenic bladder, functional outlet obstruction, and partial prostate obstruction.

3.Adverse effects: *Phenoxybenzamine* can cause postural hypotension, nasal stuffiness, inhibited ejaculation, and gastrointestinal irritation. It may also induce reflex tachycardia, which is mediated by the baroreceptor reflex. *Phenoxybenzamine* should be used with caution in patients with cerebrovascular or cardiovascular disease.

B. Phentolamine

In contrast to *phenoxybenzamine*, *phentolamine* [fen-TOLE-a-meen] is a reversible, competitive, nonselective blocker of α_1 and α_2 receptors. Effects last for approximately 4 hours after a single injection. Pharmacological effects of *phentolamine* are very similar to those of *phenoxybenzamine.* It is used for the diagnosis and short-term management of pheochromocytoma and hypertensive crisis and to prevent dermal necrosis following extravasation of *norepinephrine.* In dental and periodontal procedures, local administration of *phentolamine* can aid in reversing anesthesia of soft tissues (for example, lip and tongue) produced by injection of a local anesthetic containing a vasoconstrictor.

C. Prazosin, terazosin, and doxazosin

Prazosin [PRAY-zoe-sin], *terazosin* [ter-AY-zoe-sin], and *doxazosin* [dox-AY-zoe-sin] are selective competitive blockers of the α_1 receptor. In contrast to *phenoxybenzamine* and *phentolamine*, they are useful in the treatment of hypertension, although they are not first-line agents. [Note: *Tamsulosin* [tam-SUE-loh-sin], *alfuzosin* [al-FYOO-zoe-sin], and *silodosin* [sil-oh-

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DOE-sin] are examples of other selective α_1 antagonists indicated for the treatment of benign prostatic hyperplasia (see Chapter 43).] Metabolism leads to inactive products that are excreted in urine except for those of *doxazosin*, which appear in feces. *Doxazosin* is the longest acting of these drugs.

1.Mechanism of action: These agents decrease peripheral vascular resistance and lower blood pressure by causing relaxation of both arterial and venous smooth muscle. Unlike *phenoxybenzamine* and *phentolamine*, these drugs cause minimal changes in cardiac output, renal blood flow, and glomerular filtration rate. *Tamsulosin*, *alfuzosin*, and *silodosin* have less pronounced effects on blood pressure because they are less selective for α_{1B} receptors found in the blood vessels and more selective for α_{1A} receptors in the prostate and bladder. Blockade of the α_{1A} receptors decreases tone in the smooth muscle of the bladder neck and prostate and improves urine flow.

2.Therapeutic uses: Individuals with elevated blood pressure treated with one of these drugs do not become tolerant to its action. However, the first dose of these drugs may produce an exaggerated orthostatic hypotensive response (Figure 7.3) that can result in syncope (fainting). This action, termed a “first-dose” effect, may be minimized by adjusting the first dose to one-third or one-fourth of the normal dose and by giving the drug at bedtime. These drugs may cause modest improvement in lipid profiles and glucose metabolism in hypertensive patients. Because of inferior cardiovascular outcomes as compared with other antihypertensives, α_1 antagonists are not used as monotherapy for the treatment of hypertension (see Chapter 8).

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Figure 7.3 First dose of α_1 receptor blocker may produce an orthostatic hypotensive response that can result in syncope (fainting).

3.Adverse effects: α_1-Blockers such as *prazosin* and *doxazosin* may cause dizziness, a lack of energy, nasal congestion, headache, drowsiness, and orthostatic hypotension (although to a lesser degree than that observed with *phenoxybenzamine* and *phentolamine*). An additive hypotensive effect occurs when α_1 antagonists are given with vasodilators such as nitrates or PDE-5 inhibitors (for example, *sildenafil*), thereby necessitating cautious dose titration and

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use at the lowest possible doses. These agents may cause “floppy iris syndrome,” a condition in which the iris billows in response to intraoperative eye surgery. Figure 7.4 summarizes some adverse effects observed with α-blockers.

POLE STAR

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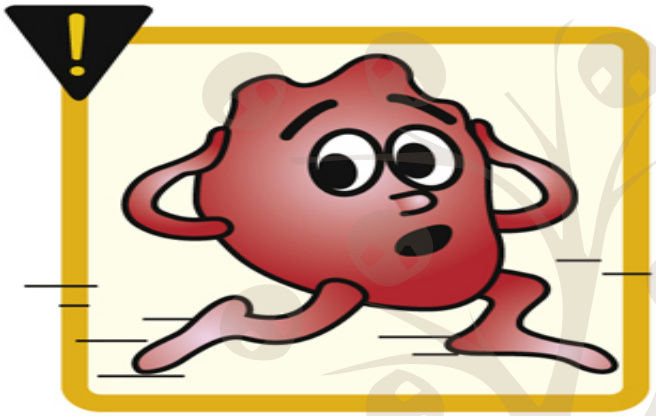
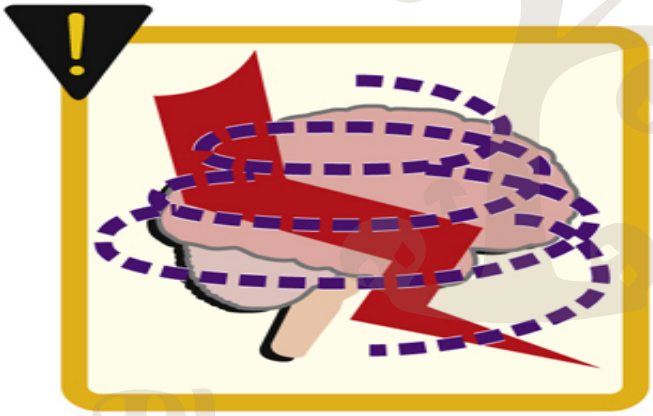
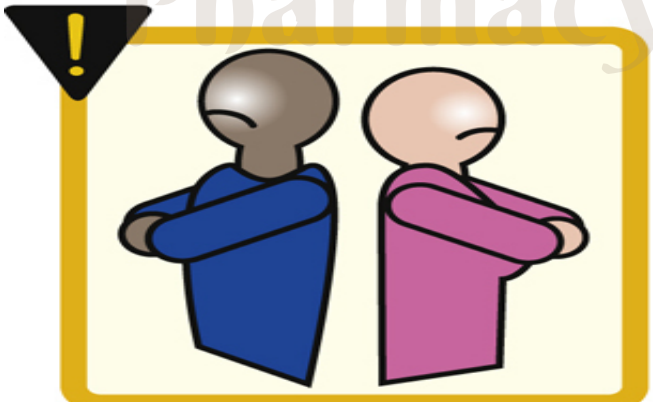
Orthostatic hypotension



Tachycardia



Dizziness and headache



Sexual dysfunction

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Figure 7.4 Some adverse effects commonly observed with α-adrenergic blocking agents.

Clinical Application 7.1: Use of α-Blockers in Benign Prostatic Hyperplasia

Benign prostatic hyperplasia (BPH) is a common condition in older men. In BPH, enlargement of the prostate can obstruct the flow of urine out of the bladder, resulting in bothersome urinary symptoms. Symptoms may include difficulty starting urination, frequent or urgent need to urinate, and increased frequency of urination at night (nocturia), among others. Lifestyle modifications, such as fluid limitation, increased exercise, and weight control may help reduce or minimize symptoms of BPH. For patients who have inadequate response to lifestyle modifications, α-blockers are a preferred drug therapy option for management of symptoms. [Note: Patients with an enlarged prostate may benefit from the addition of a 5-α reductase inhibitor; see Chapter 43.] α-Blockers antagonize adrenergic α_1 receptors found on vascular smooth muscle cells (α_{1B} effect), as well as in the urogenital smooth muscle cells (α_{1A} effect). Thus, they relax the smooth muscles in the urogenital organs, especially in the internal sphincter (bladder neck) of the bladder, urethra, and prostate. This helps to improve urine flow and symptoms associated with voiding in BPH. Since some α-blockers cause peripheral vasodilation (α_{1B} effect), they can be associated with first-dose syncope due to orthostatic hypotension, particularly drugs with less α_{1A} selectivity, such as *doxazosin* and *terazosin.* Therefore, α-blockers should be started at a low dose and titrated based on patient tolerance and improvement in symptoms.

III. B-ADRENERGIC BLOCKING AGENTS

All of the clinically available β-blockers are competitive antagonists. Nonselective β-blockers act at both β_1 and β_2 receptors, whereas cardioselective β antagonists primarily block β_1 receptors. [Note: There are no clinically useful β_2 selective antagonists.] These drugs

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also differ in intrinsic sympathomimetic activity (ISA), CNS effects, blockade of sympathetic receptors, vasodilation, and pharmacokinetics (Figure 7.5). Although all β-blockers lower blood pressure, they are less likely to induce postural hypotension, because the α-adrenoceptors remain functional. Therefore, normal sympathetic control of the vasculature is maintained and responsive to postural and activity changes. β-Blockers are effective (indications of individual drugs vary) in treating systemic as well as portal hypertension, angina, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism, tremors, and glaucoma. They are also used for the prophylaxis of migraine headaches. [Note: The names of all β-blockers end in "-olol" except for *labetalol* and *carvedilol.* Both *labetalol* and *carvedilol* also have some α-blocking actions.]

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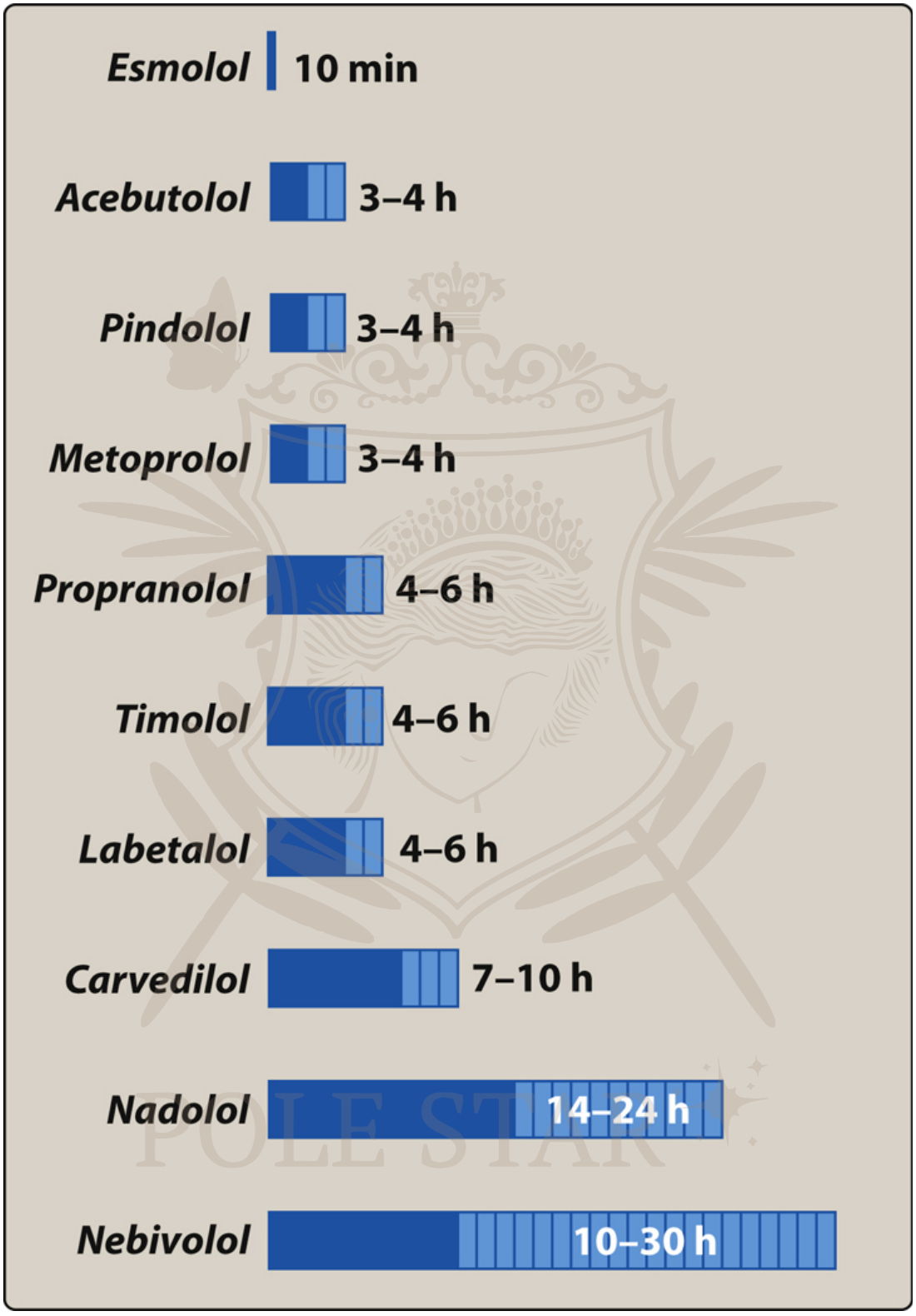

Figure 7.5 Elimination half-lives for some β-blockers.

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A. Propranolol: a nonselective β antagonist

Propranolol [proe-PRAN-oh-lole] is the prototype β-adrenergic antagonist and blocks both β_1 and β_2 receptors with equal affinity. Sustained-release preparations for once-a-day dosing are available. Nonselective β-blockers, including *propranolol*, have the ability to block the actions of *isoproterenol* (β_1, β_2 agonist) on the cardiovascular system. Thus, in the presence of a nonselective β-blocker, *isoproterenol* does not produce cardiac stimulation (β_1-mediated) or reductions in mean arterial pressure and diastolic pressure (β_2-mediated; Figure 7.2). [Note: In the presence of a nonselective β-blocker, *epinephrine* no longer lowers diastolic blood pressure or stimulates the heart, but its vasoconstrictive action (mediated by α_1 receptors) remains unimpaired. The actions of *norepinephrine* on the cardiovascular system are mediated primarily by α_1 receptors and are, therefore, mostly unaffected.]

1. Actions

a. Cardiovascular: *Propranolol* diminishes cardiac output, having both negative inotropic (decreased force of contractility) and negative chronotropic (decreased heart rate) effects (Figure 7.6). It directly depresses sinoatrial and atrioventricular nodal activity. The resulting bradycardia usually limits the dose of the drug. During exercise or stress, when the sympathetic nervous system is activated, β-blockers attenuate the expected increase in heart rate. Cardiac output, workload, and oxygen consumption are decreased by blockade of β_1 receptors, and these effects are useful in the treatment of angina (see Chapter 12). The β-blockers are effective in attenuating supraventricular cardiac arrhythmias (for example, atrial fibrillation) but generally are not effective against ventricular arrhythmias (except those induced by exercise).

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POLE STAR

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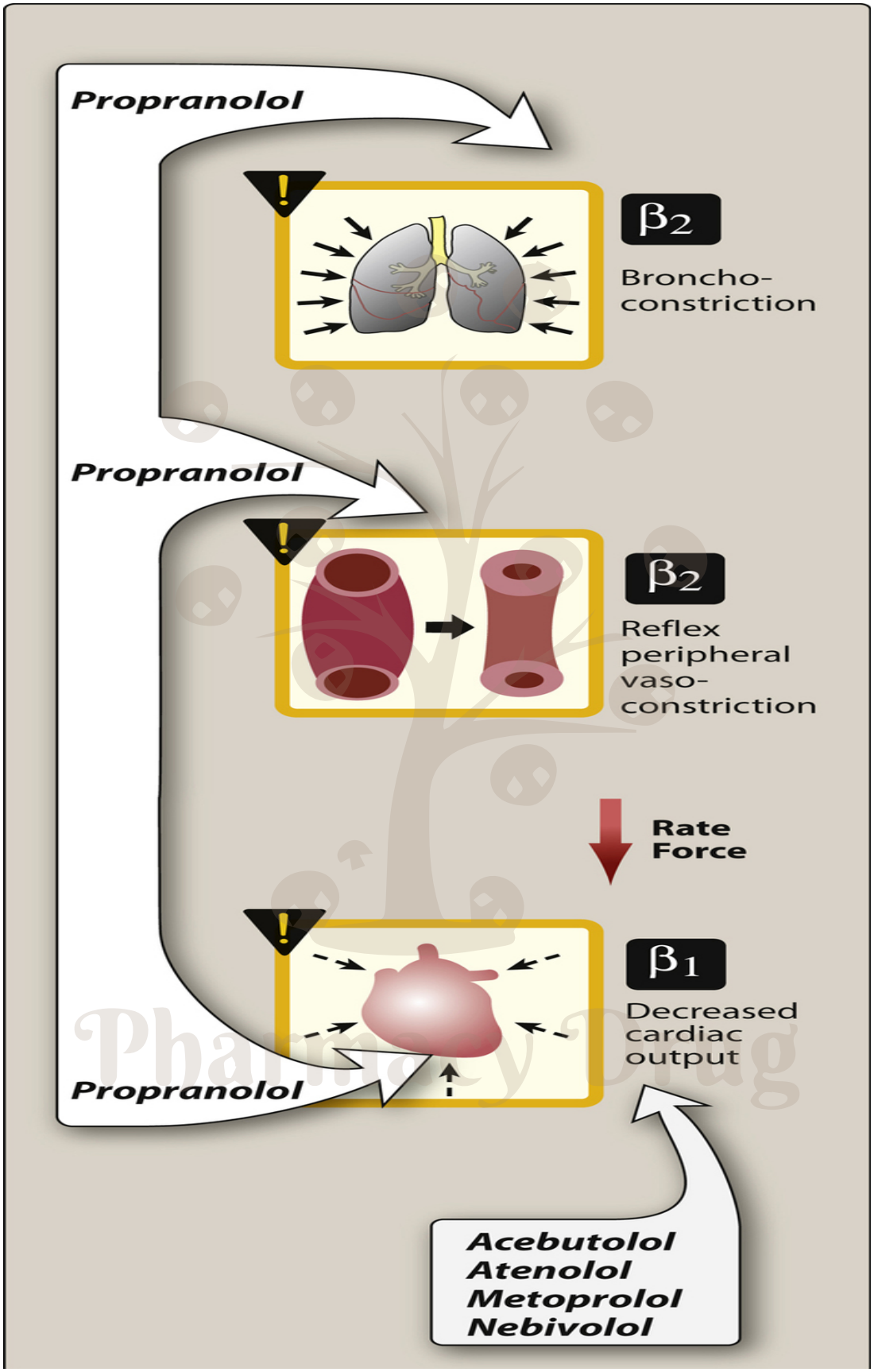

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Figure 7.6 Actions of *propranolol* and other β-blockers.

b. Peripheral vasoconstriction: Nonselective blockade of β receptors prevents β_2-mediated vasodilation in skeletal muscles, increasing peripheral vascular resistance (Figure 7.6). The reduction in cardiac output produced by all β-blockers leads to decreased blood pressure, which triggers a reflex peripheral vasoconstriction that is reflected in reduced blood flow to the periphery. In patients with hypertension, total peripheral resistance returns to normal or decreases with long-term use of *propranolol* as a result of downregulation of the β receptors. The inhibitory effect of β-blockers on renin release may also contribute to the decrease in peripheral resistance by reducing the production of angiotensin II. Clinically, there is a gradual reduction of both systolic and diastolic blood-pressures in hypertensive patients.

c. Bronchoconstriction: Blocking β_2 receptors in the lungs of susceptible patients causes contraction of the bronchiolar smooth muscle (Figure 7.6). This can precipitate an exacerbation in patients with chronic obstructive pulmonary disease (COPD) or asthma. Therefore, β-blockers, particularly nonselective ones, are contraindicated in patients with asthma and should be avoided in COPD.

d. Disturbances in glucose metabolism: β-Blockade leads to decreased glycogenolysis and decreased glucagon secretion. Therefore, if *propranolol* is given to a diabetic patient receiving *insulin*, careful monitoring of blood glucose is essential, because pronounced hypoglycemia may occur after *insulin* injection. β-Blockers also attenuate the normal physiologic response to hypoglycemia, such as tachycardia and tremors. [Note:

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Diaphoresis with hypoglycemia still occurs, as this is mediated through the neurotransmitter acetylcholine.]

2. Therapeutic uses

a. Hypertension: *Propranolol* is ineffective at reducing blood pressure in individuals with normal blood pressure. *Propranolol* lowers blood pressure in hypertension by several different mechanisms of action. Decreased cardiac output is the primary mechanism, while inhibition of renin release from the kidney, decrease in total peripheral resistance with long-term use, and decreased sympathetic outflow from the CNS are secondary contributors to the antihypertensive effects (see Chapter 8).

b. Angina pectoris: *Propranolol* decreases the oxygen requirement of heart muscle and, therefore, is effective in reducing chest pain on exertion that is common in angina. *Propranolol* is therefore useful in the management of chronic stable angina.

c. Myocardial infarction: *Propranolol* and other β-blockers have a protective effect on the myocardium. Thus, patients who have had one myocardial infarction seem to be protected against a second heart attack by prophylactic use of β-blockers. In addition, administration of a β-blocker immediately following a myocardial infarction reduces infarct size and early mortality. The mechanism for these effects may be a reduction in the actions of circulating catecholamines that increase the oxygen consumption and subsequent demand in an already ischemic heart muscle. *Propranolol* also reduces the incidence of sudden arrhythmic death after myocardial infarction.

d. Migraine: *Propranolol* is effective in reducing migraine episodes when used prophylactically (see Chapter 39). It is one of the more useful β-blockers for this indication, due to its lipophilic nature that allows it to

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penetrate the CNS. [Note: For the acute management of migraine, serotonin agonists such as *sumatriptan* are used, as well as other drugs.]

e. Hyperthyroidism: *Propranolol* and other β-blockers are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism. In acute hyperthyroidism (thyroid storm), β-blockers may be lifesaving in protecting against serious cardiac arrhythmias.

3. Pharmacokinetics: After oral administration, *propranolol* is almost completely absorbed. It is subject to first-pass effect, and only about 25% of an administered dose reaches the circulation. The volume of distribution of *propranolol* is quite large (4 L/kg), and the drug readily crosses the blood–brain barrier due to its high lipophilicity. *Propranolol* is extensively metabolized, and most metabolites are excreted in the urine.

4. Adverse effects

a. Bronchoconstriction: *Propranolol* has the potential to cause significant bronchoconstriction (Figure 7.7) due to blockade of β_2 receptors. Death by asphyxiation has been reported for patients with asthma who inadvertently received the drug. Therefore, *propranolol* is contraindicated in patients with bronchial asthma and use should be avoided in COPD.

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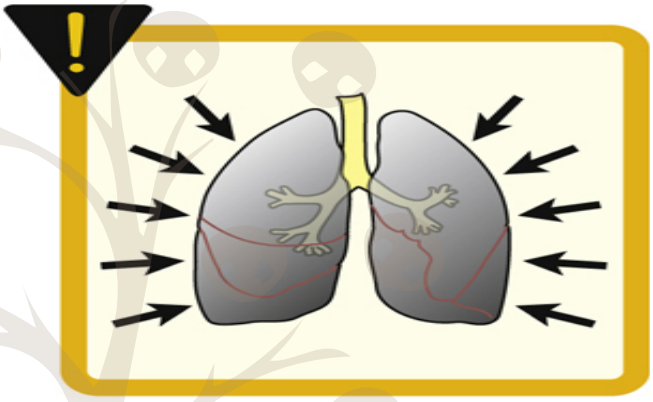
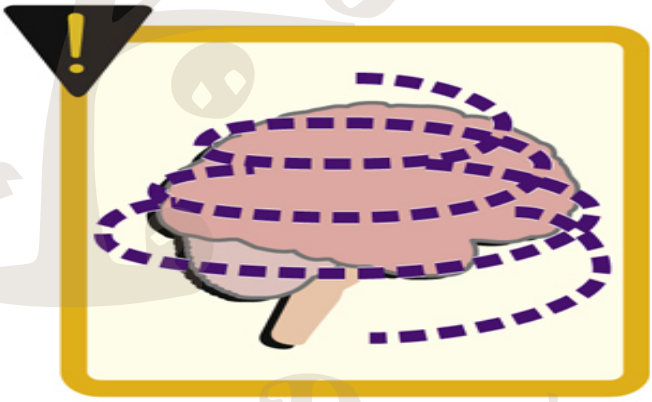
Fatigue

Broncho-
constriction



Dizziness



Arrhythmias
(upon abrupt
withdrawal)

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Figure 7.7 Adverse effects commonly observed in individuals treated with *propranolol*.

b. Arrhythmias: Treatment with β-blockers must never be stopped abruptly because of the risk of precipitating cardiac arrhythmias, which may be severe. The β-blockers must be tapered off gradually over a period of at least a few weeks. Long-term treatment with a β antagonist leads to upregulation of the β receptor. On suspension of therapy, it can precipitate worsened angina, myocardial infarction, or hypertension through action of endogenous catecholamines on the upregulated β receptors.

c. Metabolic disturbances: β-Blockade leads to decreased glycogenolysis and decreased glucagon secretion. Fasting hypoglycemia may occur. In addition, β-blockers can prevent the counterregulatory effects of catecholamines during hypoglycemia. Thus, the perception of symptoms of hypoglycemia such as tremor, tachycardia, and nervousness are blunted by β-blockers. A major role of β receptors is to mobilize energy molecules such as free fatty acids. [Note: Lipases in fat cells are activated mainly by β receptor stimulation, leading to the metabolism of triglycerides into free fatty acids.] Patients administered nonselective β-blockers may have increased triglycerides and reduced high-density lipoprotein ("good" cholesterol) through β-blockade. These effects on the serum lipid profile may be less pronounced with the use of β_1-selective antagonists such as *metoprolol*.

d. CNS effects: *Propranolol* has numerous CNS-mediated effects, including depression, dizziness, lethargy, fatigue, weakness, visual disturbances, hallucinations, short-term memory loss, emotional lability, vivid dreams (including nightmares), and depression. Fewer CNS effects

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may be seen with more hydrophilic β-blockers (for example, *atenolol*) because they do not cross the blood–brain barrier as readily.

e. Drug interactions: *Propranolol* is metabolized in the liver mainly by CYP1A2 and CYP2D6 enzymes. Therefore, inhibitors of these enzymes (for example, *bupropion*, *fluoxetine*, *paroxetine*, *quinidine*, *ritonavir*) may potentiate and inducers (for example, tobacco smoking) may diminish the antihypertensive effects of *propranolol.* In addition to this, drugs such as *amiodarone*, *diltiazem*, *disopyramide*, *dobutamine*, *dronedarone*, *flecainide*, *lidocaine*, *mefloquine*, *mexiletine*, and *verapamil* may increase the risk of cardiovascular adverse effects when given with *propranolol* through varying mechanisms. Nonselective β-blockers such as *propranolol* may prevent the bronchodilatory effects of β_2 agonists in asthma and rescue effects of *epinephrine* in anaphylaxis.

B. Nadolol and timolol: nonselective β antagonists

Nadolol [NAH-doh-lole] and *timolol* [TIM-o-lole] also block β_1- and β_2-adrenoceptors and are more potent than *propranolol. Nadolol* has a very long duration of action (Figure 7.5). *Timolol* reduces the production of aqueous humor in the eye. It is used topically in the treatment of chronic open-angle glaucoma.

1. Treatment of glaucoma: β-Blockers, such as topically applied *timolol*, are effective in diminishing intraocular pressure in glaucoma (Figure 7.8). This occurs by decreasing the secretion of aqueous humor by the ciliary body. *Carteolol* [kar-TEE-oh-lol] and *levobunolol* [lee-voe-BYOO-noe-lole] are nonselective β antagonists, whereas *betaxolol* [be-TAKS-oh-lol] is a β_1-selective agent. Unlike the cholinergic drugs, these agents neither affect the ability of the eye to focus for near vision nor change pupil size. When administered intraocularly, the onset is about 30 minutes, and the effects last for 12 to 24

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hours. The β-blockers are only used for chronic management of glaucoma. In an acute attack of glaucoma, *pilocarpine* is still the drug of choice for emergency lowering of intraocular pressure. Other agents used in the treatment of glaucoma are summarized in Figure 7.8.

CLASS OF DRUG	DRUG NAMES	MECHANISM OF ACTION	SIDE EFFECTS
β-Adrenergic antagonists (topical)	*Betaxolol, carteolol, levobunolol, timolol*	Decrease of aqueous humor production	Ocular irritation; contraindicated in patients with asthma, obstructive airway disease, bradycardia, and congestive heart failure.
α-Adrenergic agonists (topical)	*Apraclonidine, brimonidine*	Decrease of aqueous humor production and increase of aqueous outflow	Red eye and ocular irritation, allergic reactions, malaise, and headache.
Cholinergic agonists (topical)	*Pilocarpine, carbachol*	Increase of aqueous outflow	Eye or brow pain, increased myopia, and decreased vision.
Prostaglandin-like analogues (topical)	*Latanoprost, travoprost, bimatoprost*	Increase of aqueous humor outflow	Red eye and ocular irritation, increased iris pigmentation, and excessive hair growth of eye lashes.
Carbonic anhydrase inhibitors (topical and systemic)	*Dorzolamide* and *brinzolamide* (topical), *acetazolamide,* and *methazolamide* (oral)	Decrease of aqueous humor production	Transient myopia, nausea, diarrhea, loss of appetite and taste, and renal stones (oral drugs).

Figure 7.8 Classes of drugs used to treat glaucoma.

2. Portal hypertension: Nonselective β-blockers such as *nadolol* (and *propranolol*) are used in the treatment of portal hypertension in patients with cirrhosis. Treatment with these agents reduces the risk of variceal hemorrhage.

C. Acebutolol, atenolol, betaxolol, bisoprolol, esmolol, metoprolol, and nebivolol: selective β_1 antagonists

Drugs that preferentially block the β_1 receptors minimize the unwanted bronchoconstriction (β_2 effect) seen with use of nonselective agents in asthma patients. Cardioselective β-blockers, such as *acebutolol* [a-se-BYOO-toe-lol], *atenolol* [a-TEN-oh-lol], and *metoprolol* [me-TOE-proe-lol], antagonize β_1 receptors at doses 50- to 100-fold less than those required to block β_2 receptors. This cardioselectivity

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is most pronounced at low doses and is lost at high doses. [Note: Because β_1 selectivity of these agents is lost at high doses, they may antagonize β_2 receptors.]

1.Actions: These drugs lower blood pressure in hypertension and increase exercise tolerance in angina (Figure 7.6). *Esmolol* [EZ-moe-lol] has a very short half-life (Figure 7.5) due to metabolism of an ester linkage. It is only available intravenously and is used to control blood pressure or heart rhythm in critically ill patients and those undergoing surgery or diagnostic procedures. In addition to its cardioselective β-blockade, *nebivolol* [ne-BIV-oh-lol] releases nitric oxide from endothelial cells and causes vasodilation. In contrast to *propranolol*, the cardioselective β-blockers have fewer effects on pulmonary function, peripheral resistance, and carbohydrate metabolism. Nevertheless, asthma patients treated with these agents must be carefully monitored to make certain that respiratory activity is not compromised. Because these drugs have less effect on peripheral vascular β_2 receptors, coldness of extremities (Raynaud phenomenon), a common side effect of β-blockers, is less frequent.

2.Therapeutic uses: The cardioselective β-blockers are useful in hypertensive patients with impaired pulmonary function. These agents are also first-line therapy for chronic stable angina. *Bisoprolol* and the extended-release formulation of *metoprolol* (*metoprolol succinate*) are indicated for the management of chronic heart failure.

D. Acebutolol and pindolol: antagonists with partial agonist activity

1.Actions

a. Cardiovascular: *Acebutolol* (β_1-selective antagonist) and *pindolol* (nonselective β-blocker) [PIN-doe-lol] are not pure antagonists. These drugs can also weakly

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stimulate both β_1 and β_2 receptors (Figure 7.9) and are said to have ISA. These partial agonists stimulate the β receptor to which they are bound, yet they inhibit stimulation by the more potent endogenous catecholamines, epinephrine and norepinephrine. The result of these opposing actions is a diminished effect on reduction of cardiac rate and cardiac output compared with that of β-blockers without ISA.

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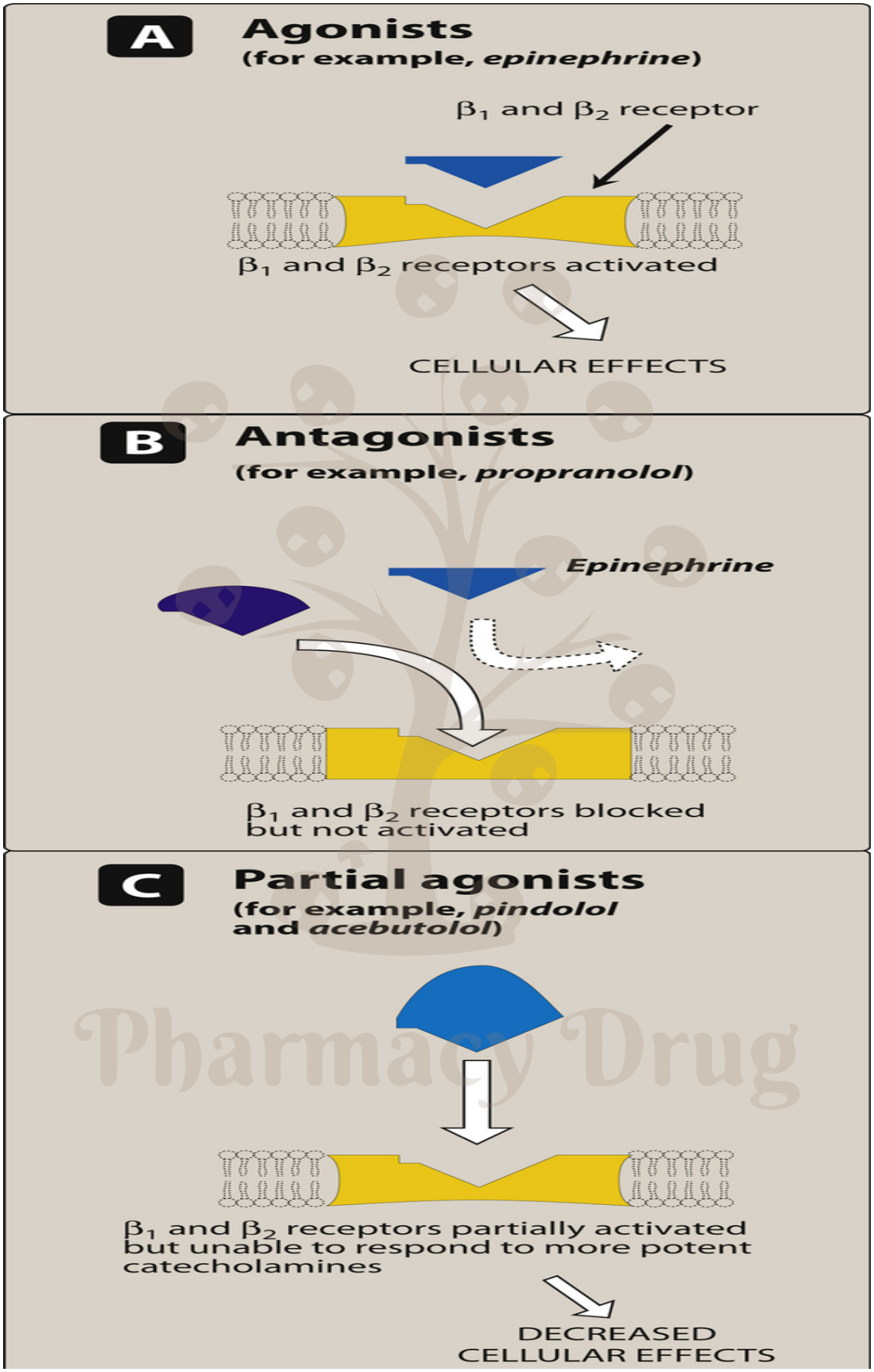

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Figure 7.9 Comparison of agonists, antagonists, and partial agonists of β-adrenoceptors.

b. Decreased metabolic effects: β-Blockers with ISA minimize the disturbances of lipid and carbohydrate metabolism that are seen with other β-blockers. For example, these agents do not decrease plasma HDL levels.

2. Therapeutic use: β-Blockers with ISA are effective in hypertensive patients with moderate bradycardia, because a further decrease in heart rate is less pronounced with these drugs. [Note: β-blockers with ISA are not used for stable angina or arrhythmias due to their partial agonist effect.] Overall, β-blockers with ISA are infrequently used in clinical practice. Figure 7.10 summarizes some of the indications for β-blockers.

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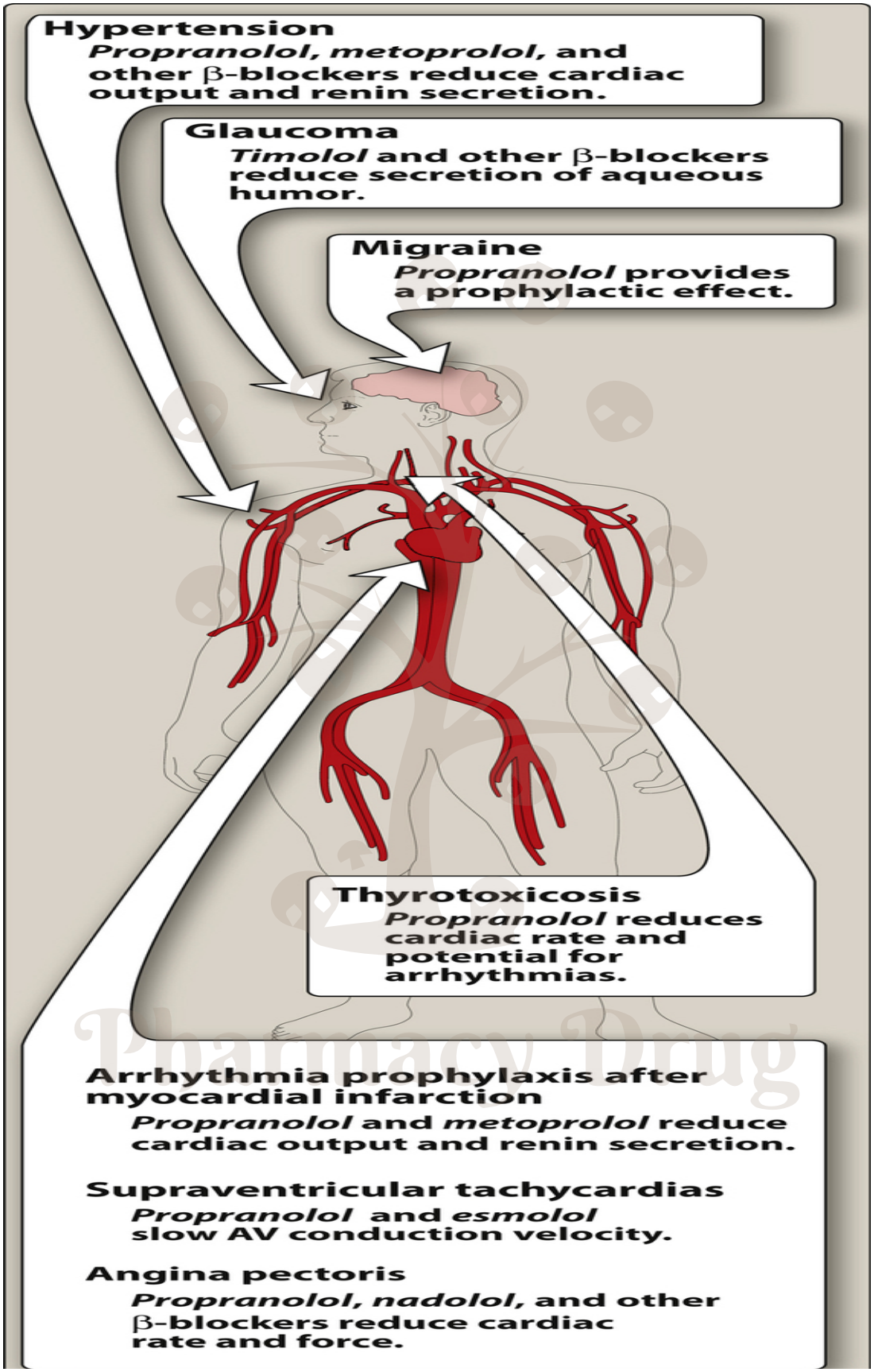

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Figure 7.10 Some clinical applications of β-blockers.AV = atrioventricular.

E. Labetalol and carvedilol: antagonists of both α- and β-adrenoceptors

1.Actions: *Labetalol* [lah-BET-a-lol] and *carvedilol* [KAR-ve-dil-ol] are nonselective β-blockers with concurrent α_1-blocking actions that produce peripheral vasodilation, thereby reducing blood pressure. They contrast with the other β-blockers that produce initial peripheral vasoconstriction, and these agents are, therefore, useful in treating hypertensive patients for whom increased peripheral vascular resistance is undesirable. *Carvedilol* also decreases lipid peroxidation and vascular wall thickening, effects that have benefit in heart failure.

2.Therapeutic uses: *Labetalol* is used as an alternative to *methyldopa* in the treatment of pregnancy-induced hypertension. Intravenous *labetalol* is also used to treat hypertensive emergencies, because it can rapidly lower blood pressure, particularly in patients with an elevated heart rate (see Chapter 8). β-Blockers should not be given to patients with an acute exacerbation of heart failure, as they can worsen the condition. However, *carvedilol* as well as *metoprolol* and *bisoprolol* are beneficial in patients with stable chronic heart failure. These agents work by blocking the effects of sympathetic stimulation on the heart, which causes worsening heart failure over time (see Chapter 10).

3.Adverse effects: Orthostatic hypotension and dizziness are associated with α_1-blockade. Figure 7.11 summarizes the receptor specificities and uses of the β-adrenergic antagonists.

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DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
Propranolol	β_1, β_2	Hypertension Migraine prophylaxis Hyperthyroidism Angina pectoris Myocardial infarction
Nadolol *Pindolol*[1]	β_1, β_2	Hypertension
Timolol	β_1, β_2	Glaucoma
Atenolol *Bisoprolol*[2] *Esmolol* *Metoprolol*[2]	β_1	Hypertension Angina Myocardial infarction Atrial fibrillation
Acebutolol[1]	β_1	Hypertension
Nebivolol	β_1, NO ↑	Hypertension
Carvedilol[2] *Labetalol*	$\alpha_1, \beta_1, \beta_2$	Hypertension

Figure 7.11 Summary of β-adrenergic antagonists.NO = nitric oxide. [1] *Acebutolol* and *pindolol* are partial agonists, as well. [2] *Bisoprolol*, *metoprolol*, and *carvedilol* are also used for the treatment of heart failure.

Clinical Application 7.2 Therapeutic Use of β-blockers

The therapeutic uses for β-blockers are many, and there are several agents from which to choose. When considering the selection of a β-blocker for therapy, it is helpful for the clinician to consider the following questions:

1. Is the β-blocker selective? Selective β-blockers preferentially antagonize β_1 receptors in the heart, making them useful for cardiac applications, such as angina, hypertension, and heart failure. Through their effect on cardiac β_1 receptors selective β-blockers reduce cardiac output, leading to a decrease in blood pressure in hypertension and a decreased myocardial oxygen consumption in angina. In addition, respiratory effects (bronchoconstriction) are minimal with cardioselective β-blockers at normal doses.
2. Is the β-blocker nonselective? Nonselective β-blockers (for example, *propranolol*) antagonize β_1 receptors found in the heart and also β_2

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receptors found in the lungs. By blocking β_2 receptors in the lungs, these agents can worsen bronchoconstriction, and they should be avoided in patients with asthma and COPD. While nonselective β-blockers are not preferred for many indications, they are considered agents of choice for management of portal hypertension in cirrhosis (for example, *nadolol*).

3. Does the β-blocker have intrinsic sympathomimetic activity (ISA)? These agents are rarely used in clinical practice (for example, *acebutolol* and *pindolol*).
4. Is the agent available in a topical formulation? Only β-blockers available in topical formulation (for example, *timolol* and *betaxolol*) are used to treat glaucoma.
5. Does the β-blocker have evidence to support its use for the desired therapeutic indication? For instance, β-blockers are used in the treatment of heart failure where they reduce workload on the myocardium and improve overall survival. Extended-release *metoprolol* (*metoprolol succinate*), *bisoprolol*, and *carvedilol* are the β-blocking agents with the greatest evidence of benefit in the treatment of heart failure. In addition, although β-blockers are not considered first-line therapy for the treatment of hypertension (see Chapter 8), they may be beneficial in treating hypertension in patients with coexisting conditions such as angina, heart failure, or supraventricular arrhythmias.

IV. DRUGS AFFECTING NEUROTRANSMITTER RELEASE OR UPTAKE

Reserpine [re-SER-peen], a plant alkaloid, blocks the Mg^{2+}/adenosine triphosphate–dependent transport of biogenic amines (norepinephrine, dopamine, and serotonin) from the cytoplasm into storage vesicles in the adrenergic nerve terminals in all body tissues. This causes the ultimate depletion of biogenic amines. Sympathetic function, in general, is impaired because of decreased release of norepinephrine. *Reserpine* has a slow onset, a long duration of action, and effects that persist for many days after discontinuation. *Reserpine* was one of the first effective drugs for treatment of hypertension; however, due to the development of

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newer and more effective agents with better side effect profiles and fewer drug interactions, *reserpine* is rarely used. It is included in this chapter because of its unique mechanism of action and historical value.

Chapter Summary

- There are two classes of adrenergic antagonists—α-blockers and β-blockers.
- α-Blockers exert their clinical effect by antagonizing α_1 receptors.
- α-Blockers (*terazosin*, *doxazosin*, *tamsulosin*, *alfuzosin*, and *silodosin*) are used mainly in the treatment of benign prostatic hyperplasia.
- α-Blockers, including *prazosin* may also be used for the treatment of hypertension, although they are not first-line agents.
- One of the major adverse effects of α-blockers is orthostatic hypotension.
- β-Blockers exert their clinical effect mainly by antagonizing β_1 receptors in the heart, resulting in decreased heart rate and contractility and a subsequent reduction in cardiac output.
- β-Blockers are used in the treatment of hypertension, stable angina, heart failure, and atrial fibrillation.
- Ophthalmic preparations of β-blockers (for example, *timolol*) are used in the treatment of glaucoma.
- Nonselective β-blockers (for example, *propranolol*) may worsen bronchoconstriction in asthma patients. Hence, cardioselective β-blockers (for example, *metoprolol*) are preferred in patients with pulmonary conditions.

STUDY QUESTIONS

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Choose the ONE best answer.

7.1 A 60-year-old man started a new antihypertensive medication. His blood pressure is well controlled, but he complains of fatigue, drowsiness, and fainting when he gets up from the bed (orthostatic hypotension). Which of the following drugs is he most likely taking?

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A. Metoprolol
B. Propranolol
C. Prazosin
D. Alfuzosin

Correct answer = C. Because they block α_1-mediated vasoconstriction, α-blockers (prazosin) are more likely to cause orthostatic hypotension as compared with β-blockers (metoprolol, propranolol). Alfuzosin is a more selective antagonist for α_{1A} receptors in the prostate and bladder and is less likely to cause hypotension than prazosin.

7.2 A 30-year-old man was brought to the emergency room with amphetamine overdose. He presented with high blood pressure and arrhythmias. Which of the following drugs is the most appropriate to treat the cardiovascular symptoms of amphetamine overdose in this patient?

A. Metoprolol
B. Prazosin
C. Nebivolol
D. Labetalol

Correct answer = D. Amphetamine is an indirect adrenergic agonist that mainly enhances the release of norepinephrine from peripheral sympathetic neurons. Therefore, it activates all types of adrenergic receptors (that is, α and β receptors) and causes an increase in blood pressure. Since both α and β receptors are activated indirectly by amphetamine, α-blockers (prazosin) or β-blockers (metoprolol, nebivolol) alone cannot relieve the cardiovascular effects of amphetamine poisoning. Labetalol blocks both α_1 and β receptors and can minimize the cardiovascular effects of amphetamine overdose.

7.3 A new antihypertensive drug was tested in an animal model of hypertension. The drug when given alone reduces blood pressure in the animal. Norepinephrine given in the presence of this drug did not cause any significant change in blood pressure or heart rate in the animal. The mechanism of action of the new drug is similar to which of the following agents?

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A. Carvedilol
B. Clonidine
C. Atenolol
D. Doxazosin

Correct answer = A. Norepinephrine activates both α_1 and β_1 receptors and causes an increase in heart rate and blood pressure. A drug that prevents the increase in blood pressure caused by norepinephrine should be similar to carvedilol that antagonizes both α_1 and β_1 receptors. Doxazosin is an α_1 antagonist, clonidine is an α_2 agonist, and atenolol is a β antagonist, and these drugs cannot completely prevent the cardiovascular effects of norepinephrine.

7.4 A β-blocker was prescribed for hypertension in a patient with asthma. After a week of treatment, the asthma attacks got worse and the patient was asked to stop taking the β-blocker. Which of the following β-blockers is an appropriate alternative that is less likely to worsen the asthma?

A. Propranolol
B. Metoprolol
C. Labetalol
D. Carvedilol

Correct answer = B. The patient was most likely given a nonselective β-blocker (antagonizes both β_1 and β_2 receptors) that made the asthma worse due to β_2 antagonism. An alternative is to prescribe a cardioselective (antagonizes only β_1) β-blocker that does not antagonize β_2 receptors in the bronchioles. Metoprolol is a cardioselective β-blocker. Propranolol, labetalol, and carvedilol are nonselective β-blockers and could worsen the asthma.

7.5 A 70-year-old man is treated with doxazosin for overflow incontinence due to his enlarged prostate. He complains of dizzy spells while getting up from bed at night. Which of the following drugs is an appropriate alternative that may not cause dizziness?

A. Propranolol

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B. Phentolamine
C. Tamsulosin
D. Terazosin

Correct answer = C. Dizziness in this elderly patient could be due to orthostatic hypotension caused by doxazosin. Tamsulosin is an α_1 antagonist that is more selective to the α_1 receptor subtype (α_{1A}) present in the prostate and less selective to the α_1 receptor subtype (α_{1B}) present in the blood vessels. Therefore, tamsulosin should not affect blood pressure significantly and may not cause dizziness. Terazosin and phentolamine antagonize both these subtypes and cause significant hypotension as a side effect. Propranolol is a nonselective β-blocker that is not indicated in overflow incontinence.

7.6 Which of the following is correct regarding β-blockers?

A. Treatment with β-blockers should not be stopped abruptly.
B. Propranolol is a cardioselective β-blocker.
C. Cardioselective β-blockers worsen asthma.
D. β-Blockers decrease peripheral resistance by causing vasorelaxation.

Correct answer = A. If β-blocker therapy is stopped abruptly, that could cause angina and rebound hypertension. This could be due to the upregulation of β receptors in the body. β-Blockers do not cause direct vasorelaxation. Therefore, they do not decrease peripheral resistance with short-term use. Propranolol is a nonselective β-blocker (not cardioselective). Cardioselective β-blockers antagonize only β_1 receptors and do not worsen asthma, as they do not-antagonize β_2 receptors.

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7.7 Which of the following drugs has the highest potential to worsen orthostatic hypotension when given together with prazosin?

A. Propranolol
B. Atenolol
C. Nebivolol

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D. Labetalol

Correct answer = D. Labetalol is a nonselective β-blocker with α_1-blocking activity. Prazosin causes orthostatic hypotension due to its α_1-blockade, which could be enhanced by adding labetalol. Propranolol, atenolol and nebivolol do not have α_1-blocking effects.

7.8 A 50-year-old man was diagnosed with exertional angina and was prescribed metoprolol and nitroglycerin. Metoprolol will help to relieve symptoms of the patient's angina mainly by which of the following mechanisms?

A. Reduced peripheral vascular resistance
B. Reduced myocardial oxygen consumption
C. Increased cardiac output
D. Relaxed coronary arteries

Correct answer = B. Metoprolol is a selective β-blocker that blocks β_1 receptors. By blocking β_1 receptors in the heart, it reduces heart rate and force of contraction that leads to reduced cardiac output and reduced oxygen consumption by the myocardium. Metoprolol does not have any direct vasorelaxant effects on the peripheral vasculature or coronary arteries; hence, it does not reduce peripheral resistance directly.

7.9 A 25-year-old woman presents with eye pain, headache, and cloudy vision and is diagnosed with open-angle glaucoma. Which of the following drugs is most appropriate to use as a topical agent to treat her symptoms?

A. Propranolol
B. Metoprolol
C. Timolol
D. Carvedilol

Correct answer = C. Among the listed drugs, timolol is the only β-blocker approved for topical use.

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7.10 A 30-year-old woman was diagnosed with migraine headache, and her physician would like to prescribe a β-blocker as a prophylactic agent in this patient. Which of the following drugs is most appropriate for this purpose?

A. Propranolol
B. Atenolol
C. Metoprolol
D. Carvedilol

Correct answer = A. Propranolol is the only β-blocker among the drug choices that is approved as a prophylactic agent in migraine. This is possibly because of the high lipophilicity of propranolol, which allows the drug to penetrate the CNS.

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Unit III:
Drugs Affecting the Cardiovascular System

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8

Antihypertensives

Benjamin Gross

I. OVERVIEW

Normal blood pressure is a systolic blood pressure less than 120 mm Hg and a diastolic blood pressure less than 80 mm Hg. Blood pressure is elevated when systolic blood pressure exceeds 120 mm Hg and diastolic blood pressure remains below 80 mm Hg. Hypertension occurs when systolic blood pressure exceeds 130 mm Hg or diastolic blood pressure exceeds 80 mm Hg on at least two occasions. Hypertension results from increased peripheral vascular arteriolar smooth muscle tone, which leads to increased arteriolar resistance and reduced capacitance of the venous system. In most cases, the cause of the increased vascular tone is unknown.

Elevated blood pressure is a common disorder, affecting approximately 45% of adults in the United States. Although many patients have no symptoms, chronic hypertension can lead to ischemic heart disease and stroke, which are the top two causes of death worldwide. Hypertension is also an important risk factor in the development of chronic kidney disease and heart failure. The incidence of morbidity and mortality significantly decreases when hypertension is diagnosed early and treated appropriately. The drugs used in the treatment of hypertension are shown in Figure 8.1. In recognition of the progressive nature of hypertension, hypertension is classified into four categories (Figure 8.2). The majority of current guidelines recommend treatment decisions based on goals of antihypertensive therapy, rather than the category of hypertension.

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DIURETICS

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Amiloride MIDAMOR
Bumetanide BUMEX
Chlorthalidone GENERIC ONLY
Eplerenone INSPRA
Ethacrynic acid EDECRIN
Furosemide LASIX
Hydrochlorothiazide MICROZIDE
Indapamide GENERIC ONLY
Metolazone ZAROXOLYN
Spironolactone ALDACTONE
Triamterene DYRENIUM
Torsemide DEMADEX

β-BLOCKERS

Acebutolol GENERIC ONLY
Atenolol TENORMIN
Betaxolol GENERIC ONLY
Bisoprolol GENERIC ONLY
Carvedilol COREG, COREG CR
Esmolol BREVIBLOC
Labetalol TRANDATE
Metoprolol LOPRESSOR, TOPROL-XL
Nadolol CORGARD
Nebivolol BYSTOLIC
Pindolol GENERIC ONLY
Propranolol INDERAL LA, INNOPRAN XL

ANGIOTENSIN II RECEPTOR BLOCKERS

Azilsartan EDARBI
Candesartan ATACAND
Irbesartan AVAPRO
Losartan COZAAR
Olmesartan BENICAR
Telmisartan MICARDIS
Valsartan DIOVAN

RENIN INHIBITORS

Aliskiren TEKTURNA

ACE INHIBITORS

Benazepril LOTENSIN
Captopril GENERIC ONLY
Enalapril VASOTEC
Fosinopril GENERIC ONLY
Lisinopril PRINIVIL, ZESTRIL
Moexipril GENERIC ONLY
Quinapril ACCUPRIL
Perindopril GENERIC ONLY
Ramipril ALTACE
Trandolapril GENERIC ONLY

CALCIUM CHANNEL BLOCKERS

Amlodipine NORVASC

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Figure 8.1 Summary of antihypertensive drugs.ACE = angiotensin converting enzyme.

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	Systolic mm Hg		Diastolic mm Hg
Normal	<120	and	<80
Elevated	120–129	or	<80
Stage 1 hypertension	130–139	or	80–89
Stage 2 hypertension	≥140	or	≥90

Figure 8.2 Classification of blood pressure.

II. ETIOLOGY OF HYPERTENSION

Although hypertension may occur secondary to other disease processes, greater than 90% of patients have essential hypertension (hypertension with no identifiable cause). A family history of hypertension increases the likelihood that an individual will develop hypertension. The prevalence of hypertension increases with age but decreases with education and income level. Non-Hispanic Blacks have a higher incidence of hypertension than do both non-Hispanic whites and Hispanic whites. Persons with diabetes, obesity, or disability status are more likely to have hypertension than those without these conditions. In addition, environmental factors, such as a stressful lifestyle, high dietary intake of sodium, and smoking, may further predispose an individual to hypertension.

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III. MECHANISMS FOR CONTROLLING BLOOD PRESSURE

Arterial blood pressure is regulated within a narrow range to provide adequate perfusion of the tissues without causing damage to the vascular system, particularly the arterial intima (endothelium). Arterial blood pressure is directly proportional to cardiac output and peripheral vascular resistance (Figure 8.3). Cardiac output and peripheral resistance, in turn, are controlled mainly by two overlapping mechanisms: (1) the underlying sympathetic activity with its corresponding baroreflexes and (2) the renin–angiotensin–aldosterone system (Figure 8.4). Most antihypertensive drugs lower blood pressure by reducing cardiac output and/or decreasing peripheral vascular resistance.

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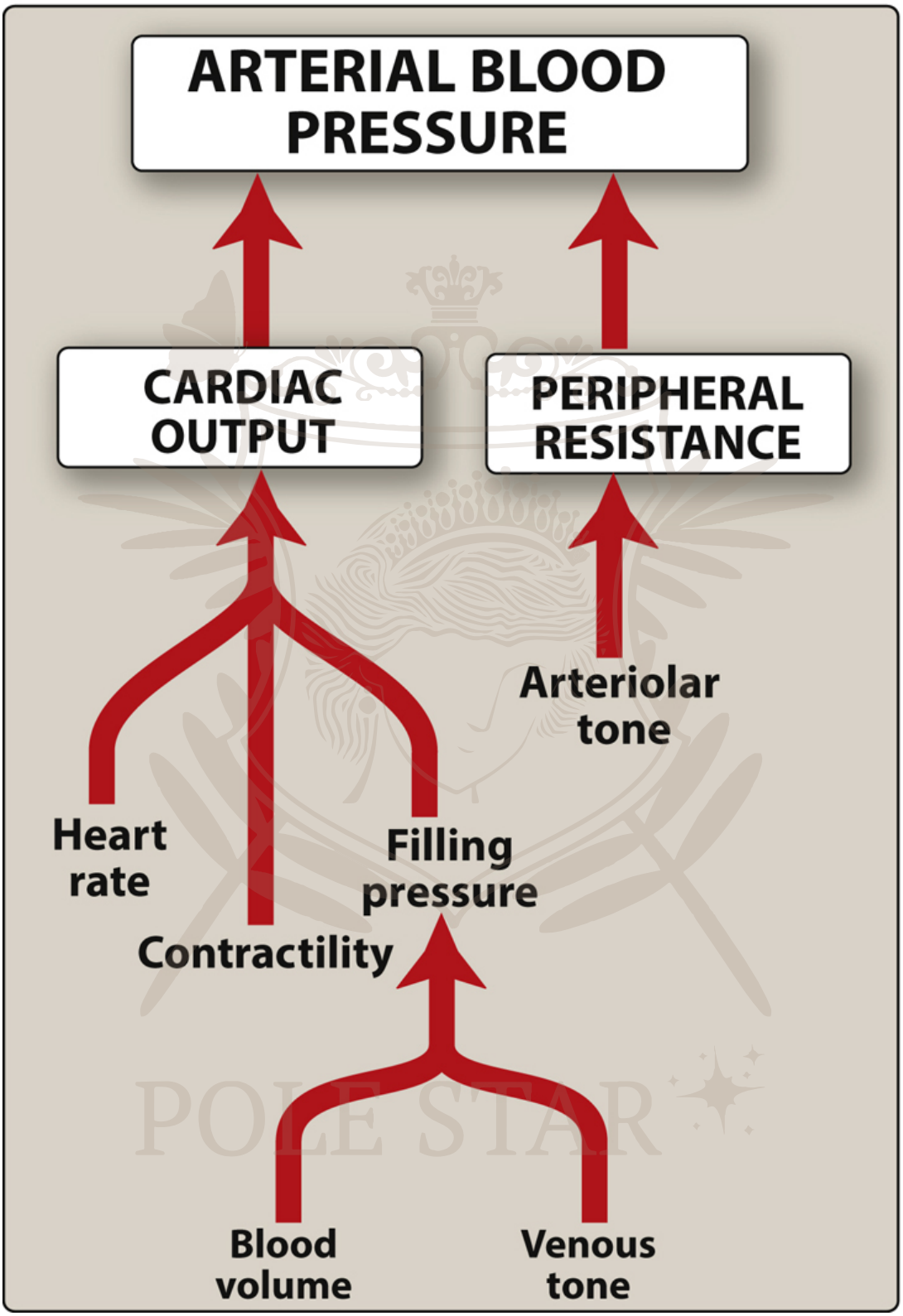

Figure 8.3 Major factors influencing blood pressure.

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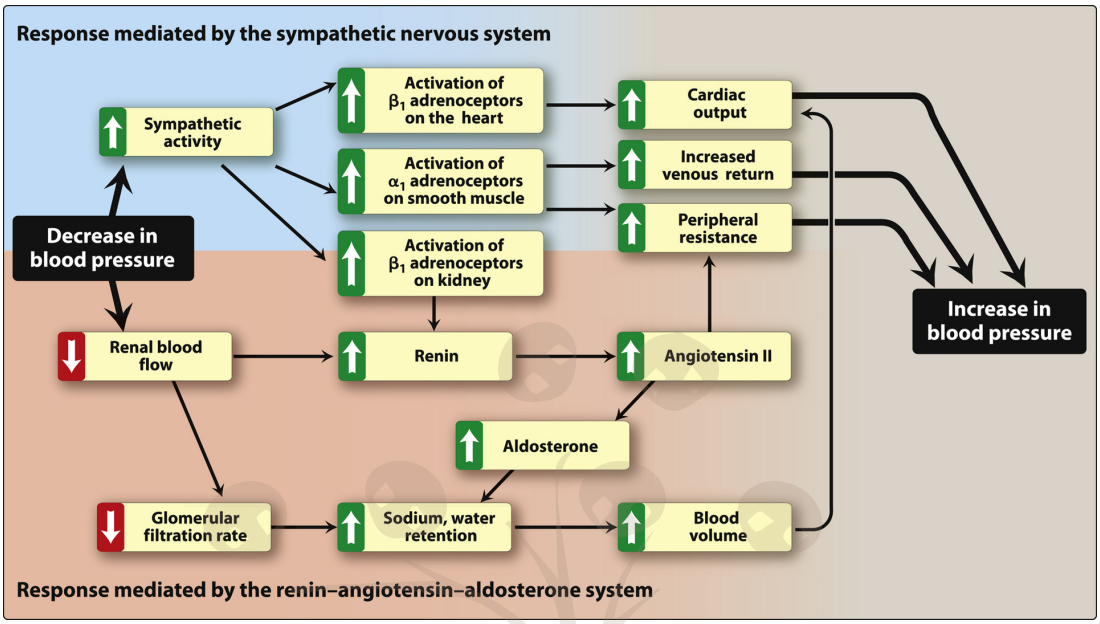

Figure 8.4 Response of the autonomic nervous system and the renin–angiotensin–aldosterone system to a decrease in blood pressure.

A. Autonomic nervous system

The autonomic nervous system is primarily responsible for regulation of blood pressure, which is a combination of cardiac output and systemic vascular resistance. Cardiac output results from a combination of chronotropic, inotropic, lusitropic, and dromotropic activity, combined with an adjustable ventricular preload that dictates the volume of blood ejected from the heart. [Note: Chronotropic relates to heart rate (for example, increase in heart rate can increase cardiac output); inotropic relates to force of contractility; lusitropic is the rate of heart relaxation, and dromotropic is conduction speed.] These cardiac output variables are primarily controlled by the underlying sympathetic activity in conjunction with its counteracting parasympathetic forces. Ventricular preload can be altered by (1) directly acting catecholamines emanating from the sympathetic system that shift fluid from peripheral to central compartments, (2) parasympathetic activity that vasodilates and reduces preload, or (3) hormonal activity sourced from the renin–angiotensin–aldosterone system. The rapid, moment-to-moment regulation of blood pressure is a direct result of the both the sympathetic and parasympathetic

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actions, coupled to the baroreflexes that function to mitigate the abruptly changing physiology. For instance, a fall in blood pressure causes pressure-sensitive neurons (baroreceptors in the aortic arch and carotid sinuses) to send fewer impulses to cardiovascular centers in the spinal cord. This prompts a reflex response of increased sympathetic and decreased parasympathetic output to the heart and vasculature, resulting in vasoconstriction and increased cardiac output. These changes result in a compensatory rise in blood pressure (Figure 8.4). The autonomic activity of the sympathetic and parasympathetic systems also directly impacts the changing resistance within the systemic vasculature, which directly increases or decreases vascular tone and subsequent blood pressure.

B. Renin–angiotensin–aldosterone system

The kidney provides long-term hormonal control of blood pressure by altering the blood volume within the vascular system. Baroreceptors in the kidney respond to reduced arterial pressure (and to sympathetic stimulation of β_1-adrenoceptors) by releasing the enzyme renin (Figure 8.4). Low sodium intake and greater sodium loss can also increase renin release. Renin converts angiotensinogen to angiotensin I, which is converted in turn to angiotensin II, in the presence of angiotensin converting enzyme (ACE). Angiotensin II is a potent circulating vasoconstrictor, constricting both arterioles and veins and resulting in an increase in blood pressure. Angiotensin II exerts a preferential vasoconstrictor action on the efferent arterioles of the renal glomerulus, increasing glomerular filtration. Furthermore, angiotensin II stimulates aldosterone secretion, leading to increased renal sodium reabsorption, and subsequently an increased blood volume, which contributes to an increase in the blood pressure. These effects of angiotensin II are mediated by stimulation of angiotensin II type 1 (AT_1) receptors.

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Clinical Application 8.1 Mechanism of Controlling Blood Pressure

Controlling cardiac output and/or peripheral vascular resistance by two overlapping mechanisms can be key to controlling blood pressure. Catecholamines released as a result of sympathetic activity stimulate α_1 receptors in the periphery (vasoconstriction and increased peripheral vascular resistance) and β_1 receptors in the heart

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(increased heart rate, contractility, and cardiac output), resulting in increased blood pressure. Administration of agents that block α_1 or β_1 receptors mitigates the immediate and short-acting changes and establishes short-term control of elevated cardiac output and peripheral vascular resistance. The kidneys provide long-term control of blood pressure by also utilizing baroreceptors, hence the overlapping mechanisms. A fall in blood pressure results in release of the enzyme renin as part of the renin–angiotensin–aldosterone system (Figure 8.4). Ultimately, this leads to the production of angiotensin II, which is a potent vasoconstrictor. Angiotensin II also stimulates aldosterone secretion, further increasing blood pressure. Some of these compensatory mechanisms are dysfunctional in individuals with hypertension and, thus, are a target for treatment.

IV. TREATMENT STRATEGIES

The goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality. For most patients, the blood pressure goal when treating hypertension is a systolic blood pressure of less than 130 mm Hg and a diastolic blood pressure of less than 80 mm Hg. Current recommendations are to initiate therapy with a thiazide diuretic, ACE inhibitor, angiotensin receptor blocker (ARB), or calcium channel blocker (CCB). However, recommendations for initial drug therapy may vary depending on the guideline, concomitant disease states, and patient age (Figure 8.5). If blood pressure is inadequately controlled, a second antihypertensive drug from another class should be added, with selection based on achieving the goal blood pressure and minimizing the adverse effects of the combined regimen. Patients with systolic blood pressure greater than 20 mm Hg above goal or diastolic blood pressure more than 10 mm Hg above goal should be started on two antihypertensives simultaneously. Combination therapy with separate agents or a fixed-dose combination pill may lower blood pressure more quickly with fewer adverse effects. Fixed-dose combination pills contain antihypertensives from different classes. A variety of fixed-dose combination therapies are available to increase the ease of patient adherence to treatment regimens that require multiple medications.

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GUIDELINES	POPULATION DEMOGRAPHICS	GOAL BLOOD PRESSURE	INITIAL DRUG THERAPY OPTIONS
ACC/AHA 2017	General nonelderly	<130/80	Nonblack: thiazide diuretic, ACE inhibitor, ARB, CCB Black: thiazide diuretic or CCB
	Elderly >65 years old	<130/80	Use clinical judgment on blood pressure goal and drug choice if serious comorbidities
ADA 2021	Diabetes	<140/90 <130/80 (High ASCVD risk)	ACE inhibitor or ARB
KDIGO 2020	CKD	SBP < 120	ACE inhibitor or ARB
ESH/ESC 2018	< 65 years old	<130/80	ACE or ARB + CCB OR ACE or ARB + thiazide diuretic
	< 65 years old plus CKD > 65 years old	< 130-139/70-79	
	Diabetes	< 130-139/70-79	
NICE 2019	>80 years old	<150/90	≥55 years old or Black: CCB
	<80 years old	<140/90	<55 years old: ACE inhibitor or ARB

Figure 8.5 Comparison of blood pressure goals and initial drug therapy with various guidelines for hypertension.ACC = American College of Cardiology; ACE = angiotensin converting enzyme; ADA = American Diabetes Association; AHA = American Heart Association; ARB = angiotensin receptor blocker; ASCVD = atherosclerotic cardiovascular disease; CCB = calcium channel blocker; CKD = chronic kidney disease; ESC = European Society of Cardiology; ESH = European Society of Hypertension; KDIGO = Kidney Disease: Improving Global Outcomes; NICE = National Institute for Health and Care Excellence; SBP = systolic blood pressure.

A. Individualized care

Hypertension may coexist with other conditions that can be aggravated by some of the antihypertensive drugs or that may benefit from the use of some antihypertensive drugs independent of blood pressure control. In such cases, it is important to tailor the antihypertensive regimen to the patient. Figure 8.6 shows preferred therapies in hypertensive patients with concomitant diseases.

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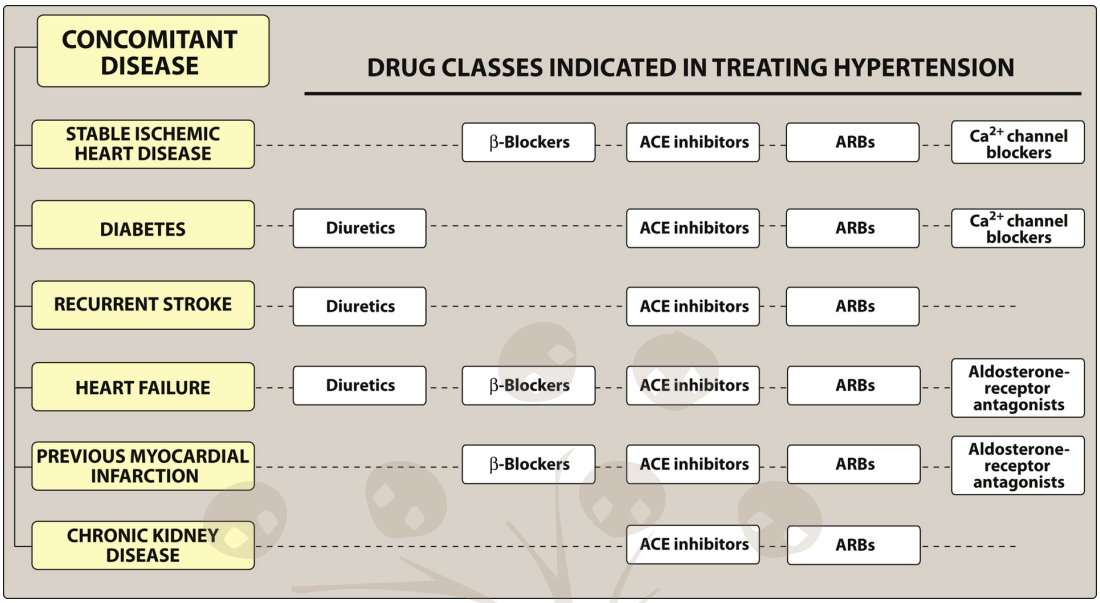

Figure 8.6 Treatment of hypertension in patients with concomitant diseases. [Note: Angiotensin receptor blockers (ARBs) are an alternative to angiotensin converting enzyme (ACE) inhibitors.]

Clinical Application 8.2: Treatment Strategies for Hypertension

For most patients, a blood pressure goal of less than 130/80 mm Hg is sufficient and supported by current guidelines. Selection of initial drug therapy does vary per guideline, but most guidelines recommend using either a thiazide diuretic, ACE inhibitor, ARB, or calcium channel blocker. In some instances, comorbid diseases may lead the clinician to choose an agent that is not one of the recommended first-line treatments, such as a β-blocker. Likewise, there are situations in which choosing a first-line medication would be inappropriate. For example, ACE inhibitors and ARBs are a poor choice in a patient with a history of angioedema, and non-dihydropyridine calcium channel blockers may be detrimental in patients with heart failure with reduced ejection fraction. Individualizing care for the hypertensive patient is important to improve clinical outcomes, reduce medication burden, and limit adverse effects.

V. DIURETICS

For all classes of diuretics, the initial mechanism of action is based upon decreasing blood volume, which ultimately leads to decreased blood pressure. Routine serum electrolyte monitoring should be done for all

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patients receiving diuretics. A complete discussion of the actions, therapeutic uses, pharmacokinetics, and adverse effects of diuretics can be found in Chapter 9.

A. Thiazide diuretics

Thiazide diuretics, such as *hydrochlorothiazide* [hye-droe-klor-oh-THYE-a-zide] and thiazide-like diuretics, such as *chlorthalidone* [klor-THAL-ih-done], lower blood pressure initially by increasing sodium and water excretion. This causes a decrease in intravascular volume, resulting in a decrease in cardiac output and renal blood flow (Figure 8.7). With long-term treatment, plasma volume approaches a normal value, but a hypotensive effect persists that is related to a direct decrease in peripheral vascular resistance that occurs after a few weeks of therapy. Thiazide diuretics can be used as initial drug therapy for hypertension unless there are compelling reasons to choose another agent. Thiazides are useful in combination therapy with a variety of other antihypertensive agents, including β-blockers, ACE inhibitors, ARBs, and potassium-sparing diuretics. With the exception of *metolazone* [me-TOL-ah-zone], thiazide diuretics are not effective in patients with inadequate kidney function (estimated glomerular filtration rate less than 30 mL/min/m^2). Loop diuretics may be required in these patients. Thiazide diuretics can induce hypokalemia, hyperuricemia, and, to a lesser extent, hyperglycemia in some patients.

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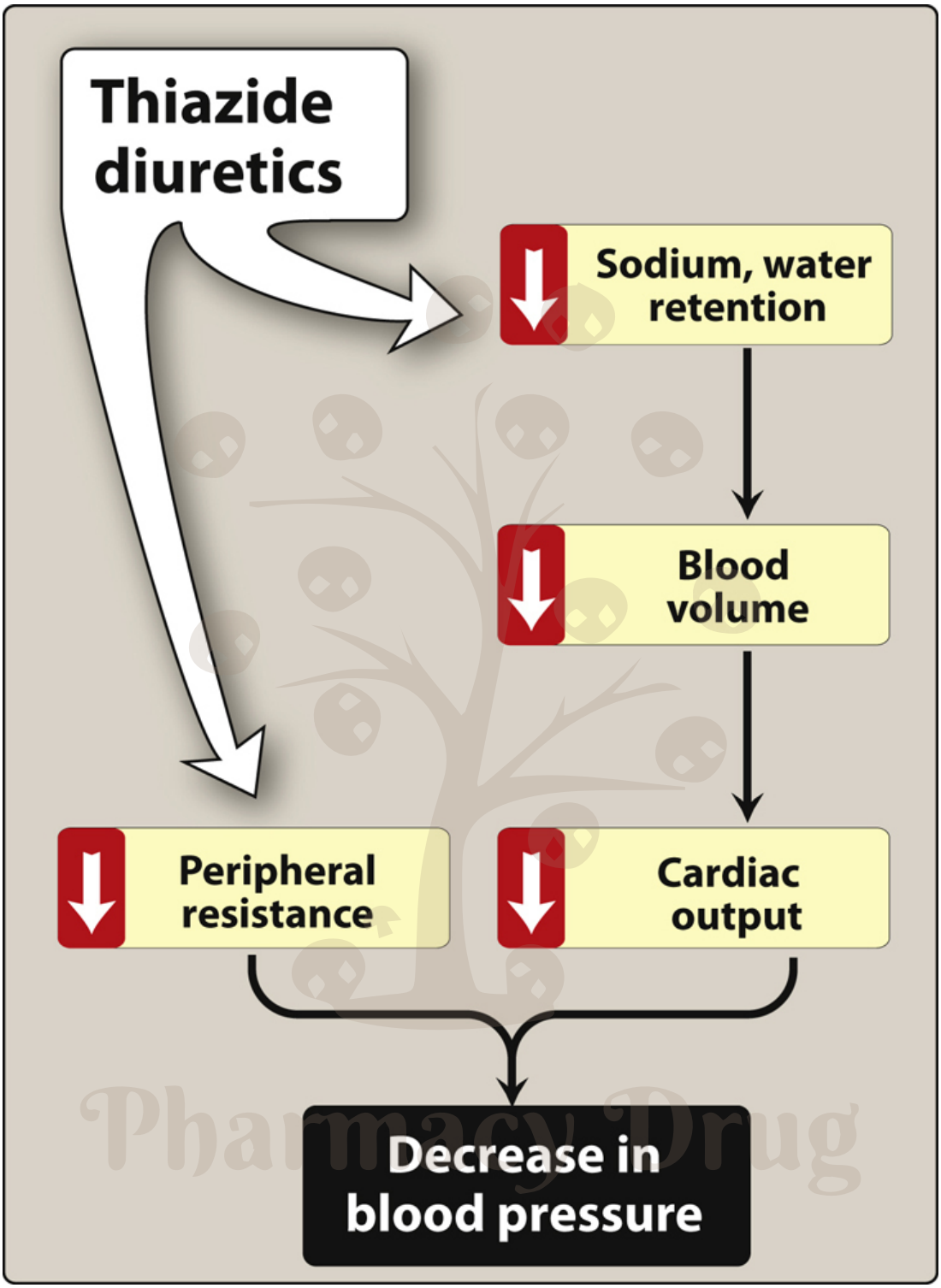

Figure 8.7 Actions of thiazide diuretics.

B. Loop diuretics

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The loop diuretics *furosemide*, *torsemide*, *bumetanide*, and *ethacrynic acid* act promptly by blocking sodium and chloride reabsorption in the kidneys. Loop diuretics cause decreased renal vascular resistance and increased renal blood flow. These agents produce diuresis, even in patients with poor renal function and those who have not responded to thiazide diuretics. Like thiazide diuretics, they can cause hypokalemia. Loop diuretics increase the excretion of calcium in the urine and can cause hypocalcemia, whereas thiazide diuretics reduce calcium excretion and may contribute to increased plasma calcium levels. Loop diuretics are rarely used alone to treat hypertension, but they are commonly used to manage symptoms of heart failure and peripheral edema.

C. Potassium-sparing diuretics

Amiloride [a-MIL-oh-ride] and *triamterene* [tri-AM-ter-een] are inhibitors of epithelial sodium transport at the late distal and collecting ducts, and *spironolactone* [speer-on-oh-LAK-tone] and *eplerenone* [eh-PLEH-reh-none] are aldosterone receptor antagonists. All of these agents reduce potassium loss in the urine. Aldosterone antagonists have the additional benefit of improving cardiac remodeling of the ventricles in patients with systolic heart failure (see Chapter 10). Potassium-sparing diuretics are sometimes used in combination with loop diuretics and thiazides to reduce the amount of potassium loss induced by these diuretics.

VI. B-ADRENOCEPTOR–BLOCKING AGENTS

β-Blockers are a treatment option for hypertensive patients, and can be particularly helpful for those patients with concomitant heart disease or heart failure (Figure 8.6).

A. Actions

The β-blockers reduce blood pressure primarily by decreasing cardiac output via a reduction in chronotropic, inotropic, and lusitropic activity (Figure 8.8). They may also decrease sympathetic outflow from the central nervous system (CNS), thereby inhibiting the release of renin

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from the kidneys and subsequently decreasing the formation of angiotensin II and the secretion of aldosterone. The prototype β-blocker is *propranolol* [proe-PRAN-oh-lol], which acts at both β_1 and β_2 receptors. Selective blockers of β_1 receptors, such as *metoprolol* [me-TOE-pro-lol] and *atenolol* [ah-TEN-oh-lol], are among the most commonly prescribed β-blockers. *Nebivolol* [ne-BIV-oh-lole] is a selective blocker of β_1 receptors, which also increases the production of nitric oxide, leading to peripheral vasodilation. The selective β-blockers should be used with caution in hypertensive patients who also have asthma; however, nonselective β-blockers are contraindicated due to their blockade of β_2-mediated bronchodilation (See Chapter 7 for an in-depth discussion of β-blockers.). β-Blockers should be used cautiously in the treatment of patients with acute heart failure or peripheral vascular disease.

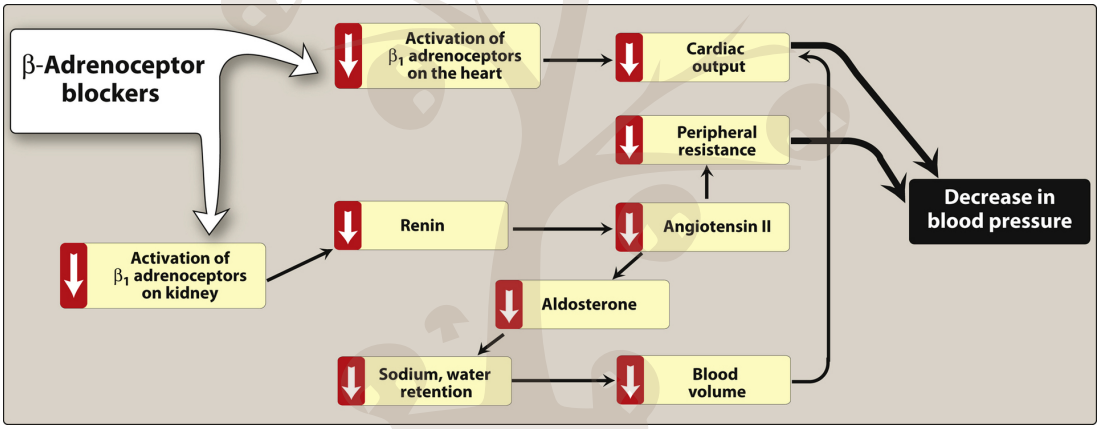

Figure 8.8 Actions of β-adrenoceptor–blocking agents.

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B. Therapeutic uses

The primary therapeutic benefits of β-blockers are seen in hypertensive patients with concomitant heart disease, such as supraventricular tachyarrhythmia (for example, atrial fibrillation), previous myocardial infarction, stable ischemic heart disease, and chronic heart failure. Conditions that discourage the use of β-blockers include reversible bronchospastic disease such as asthma,

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bradycardia, second- and third-degree heart block, and severe peripheral vascular disease.

C. Pharmacokinetics

The β-blockers are orally active for the treatment of hypertension. *Propranolol* undergoes extensive and highly variable first-pass metabolism. Oral β-blockers may take several weeks to achieve full therapeutic effects. *Esmolol*, *metoprolol*, and *propranolol* are available in intravenous formulations.

D. Adverse effects

β-Blockers reduce heart rate and may result in bradycardia, hypotension, and reduced exercise tolerance. Nonselective β-blockers may disturb lipid metabolism, decreasing high-density lipoprotein cholesterol and increasing triglycerides. Lipophilic agents, such as *propranolol*, may penetrate the CNS and lead to nightmares or difficulty sleeping (see Chapter 7). Abrupt withdrawal of β-blockers may induce severe rebound hypertension, angina, myocardial infarction, and even sudden death in patients with ischemic heart disease. Therefore, these drugs must be tapered over a few weeks in patients with hypertension and ischemic heart disease. Figure 8.9 describes some of the adverse effects of β-blockers.

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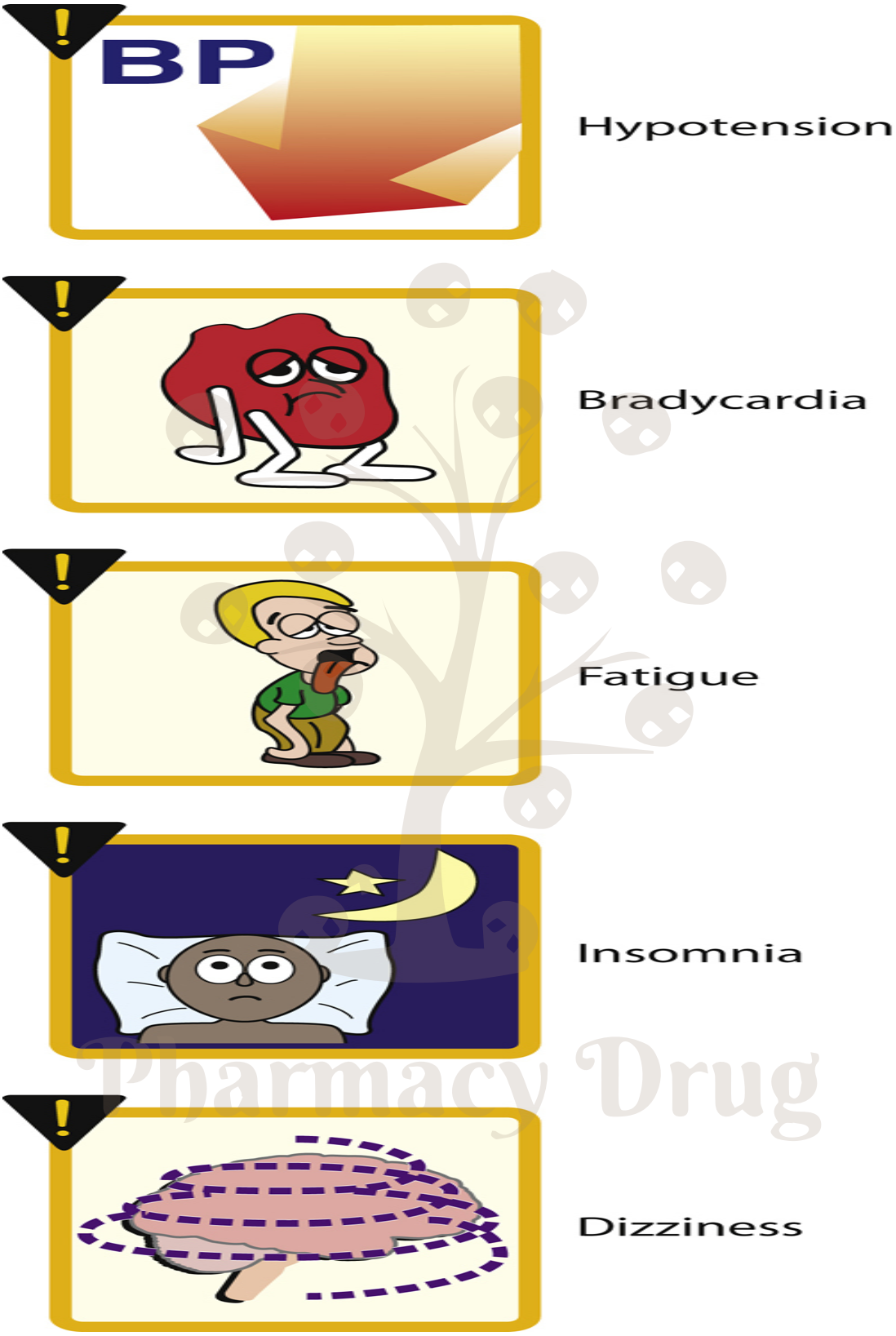

Figure 8.9 Some adverse effects of β-blockers.

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VII. ACE INHIBITORS

ACE inhibitors such as *captopril* [KAP-toe-pril], *enalapril* [e-NAL-ah-pril], and *lisinopril* [lye-SIN-oh-pril] are recommended as first-line treatment of hypertension in patients with a variety of compelling indications, including history of coronary artery disease, diabetes, stroke, heart failure, myocardial infarction, or chronic kidney disease (Figure 8.6).

A. Actions

The ACE inhibitors lower blood pressure by reducing peripheral vascular resistance. These drugs block the enzyme ACE, which cleaves angiotensin I to form the potent vasoconstrictor angiotensin II (Figure 8.10). ACE is also responsible for the breakdown of bradykinin, a peptide that increases the production of nitric oxide and prostacyclin by the blood vessels. Both nitric oxide and prostacyclin are potent vasodilators. Administration of ACE inhibitors results in vasodilation of both arterioles and veins. This occurs as a result of decreased vasoconstriction (from diminished levels of angiotensin II) and enhanced vasodilation (from increased bradykinin). By reducing circulating angiotensin II levels, ACE inhibitors also decrease the secretion of aldosterone, resulting in decreased sodium and water retention. Subsequently, ACE inhibitors reduce both cardiac preload and afterload, thereby decreasing myocardial workload. In addition, beneficial effects on renal function may result from efferent arteriolar vasodilation and decreased intraglomerular pressures.

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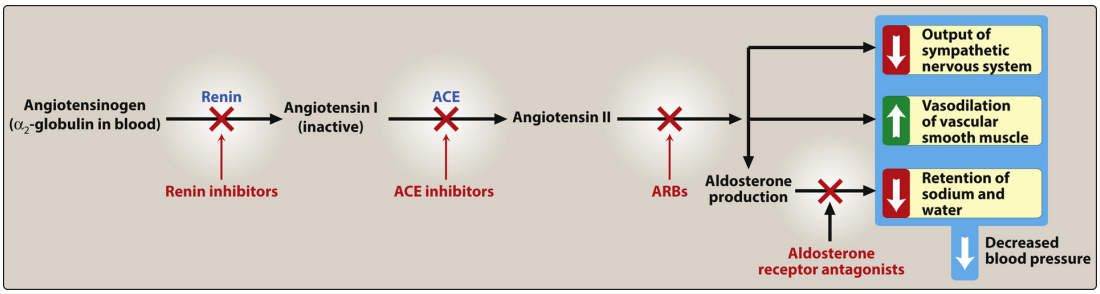

Figure 8.10 Effects of various drug classes on the renin–angiotensin–aldosterone system.*Blue* = drug target enzymes; *red* = drug class.

B. Therapeutic uses

ACE inhibitors are a preferred drug class for initial management of hypertension. All ACE inhibitors are equally effective in the treatment of hypertension at equivalent doses. ACE inhibitors slow the progression of diabetic nephropathy and decrease albuminuria, which supports their use in patients with diabetic nephropathy. Chronic treatment with ACE inhibitors achieves sustained blood pressure reduction, regression of left ventricular hypertrophy, and improved ventricular remodeling after a myocardial infarction. ACE inhibitors are a standard in the care of a patient following a myocardial infarction and first-line agents in the treatment of patients with systolic dysfunction. ACE inhibitors are first-line drugs for treating heart failure, hypertensive patients with chronic kidney disease, and patients at increased risk of coronary artery disease.

C. Pharmacokinetics

All of the ACE inhibitors are orally bioavailable as a drug or prodrug. All but *captopril* and *lisinopril* undergo hepatic conversion to active metabolites, so these agents may be preferred in patients with severe hepatic impairment. *Fosinopril* [foe-SIN-oh-pril] is the only ACE inhibitor that is not eliminated primarily by the kidneys. Therefore, it does not require dose adjustment in patients with renal impairment. *Enalaprilat* [en-AL-a-pril-AT] is the only drug in this class available intravenously.

D. Adverse effects

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Figure 8.11 describes some of the common adverse effects of ACE inhibitors. Dry cough, which occurs in up to 10% of patients, is thought to be due to increased levels of bradykinin and substance P in the pulmonary tree. The cough occurs more frequently in women, and it usually resolves within a few days of discontinuation. Angioedema, a rare but potentially life-threatening reaction that causes swelling of the lips, oral mucosa, and throat, likely results from increased levels of bradykinin. Due to a decrease in aldosterone production, potassium excretion is reduced with use of ACE inhibitors. Potassium levels must be monitored while on ACE inhibitors, and potassium supplements and potassium-sparing diuretics should be used with caution due to the risk of hyperkalemia. Serum creatinine levels should also be monitored, particularly in patients with underlying renal disease. However, an increase in serum creatinine of up to 30% above baseline after initiation of therapy with ACE inhibitors is acceptable and, by itself, does not warrant discontinuation of treatment. ACE inhibitors can induce fetal malformations and should not be used by pregnant women.

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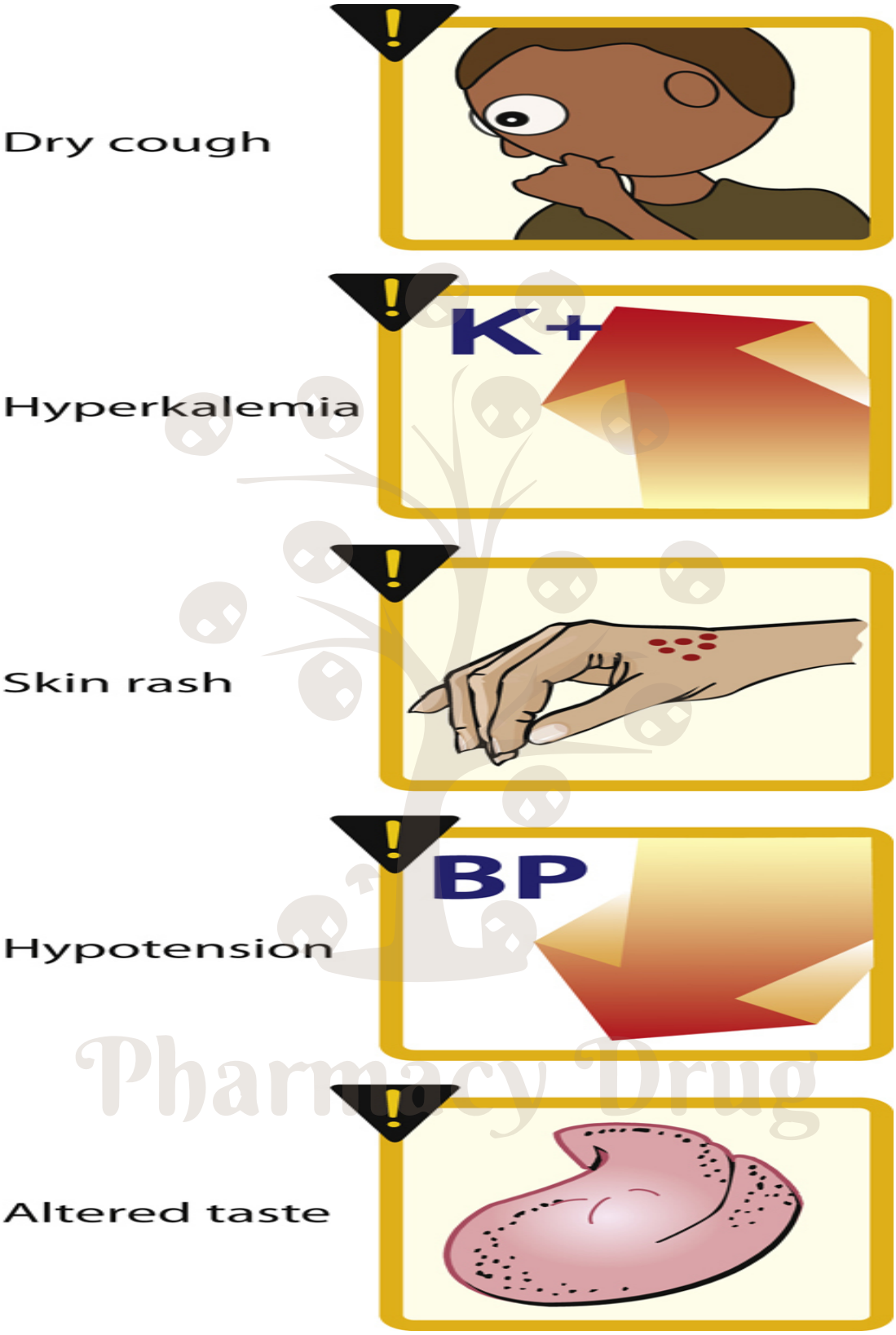

Figure 8.11 Some common adverse effects of the ACE inhibitors.

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VIII. ANGIOTENSIN II RECEPTOR BLOCKERS

The ARBs, such as *losartan* [LOW-sar-tan] and *irbesartan* [ir-be-SAR-tan], block the AT_1 receptors, decreasing the activation of AT_1 receptors by angiotensin II. Their pharmacologic effects are similar to those of ACE inhibitors in that they produce arteriolar and venous dilation and block aldosterone secretion, thus lowering blood pressure and ventricular preload by decreasing salt and water retention (Figure 8.10). ARBs do not increase bradykinin levels. They may be used as first-line agents for the treatment of hypertension, especially in patients with coexisting diabetes, heart failure, or chronic kidney disease (Figure 8.6). Adverse effects are similar to those of ACE inhibitors, although the risks of cough and angioedema are significantly decreased. ARBs should not be combined with an ACE inhibitor for the treatment of hypertension due to similar mechanisms of action and adverse effects. These agents are also teratogenic and should not be used by pregnant women. [Note: The ARBs are discussed more fully in Chapter 10.]

IX. RENIN INHIBITOR

A selective renin inhibitor, *aliskiren* [a-LIS-ke-rin], is approved for the treatment of hypertension. *Aliskiren* directly inhibits renin and, thus, acts earlier in the renin–angiotensin–aldosterone system than ACE inhibitors or ARBs (Figure 8.10). *Aliskiren* should not be combined with an ACE inhibitor or ARB in the treatment of hypertension. *Aliskiren* can cause diarrhea, especially at higher doses. Cough and angioedema may also occur, but at lower frequency than with ACE inhibitors. As with ACE inhibitors and ARBs, *aliskiren* is contraindicated during pregnancy. *Aliskiren* is metabolized by CYP3A4 and is subject to many drug interactions.

X. CALCIUM CHANNEL BLOCKERS

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Calcium channel blockers are a recommended first-line treatment option in Black patients. They may also be useful in hypertensive patients with diabetes or stable ischemic heart disease. High doses of short-acting calcium channel blockers should be avoided because of increased risk of myocardial infarction due to excessive vasodilation and marked reflexive baroreceptor cardiac activity.

A. Classes of calcium channel blockers

The calcium channel blockers are divided into three chemical classes, each with different pharmacologic properties and clinical indications (Figure 8.12).

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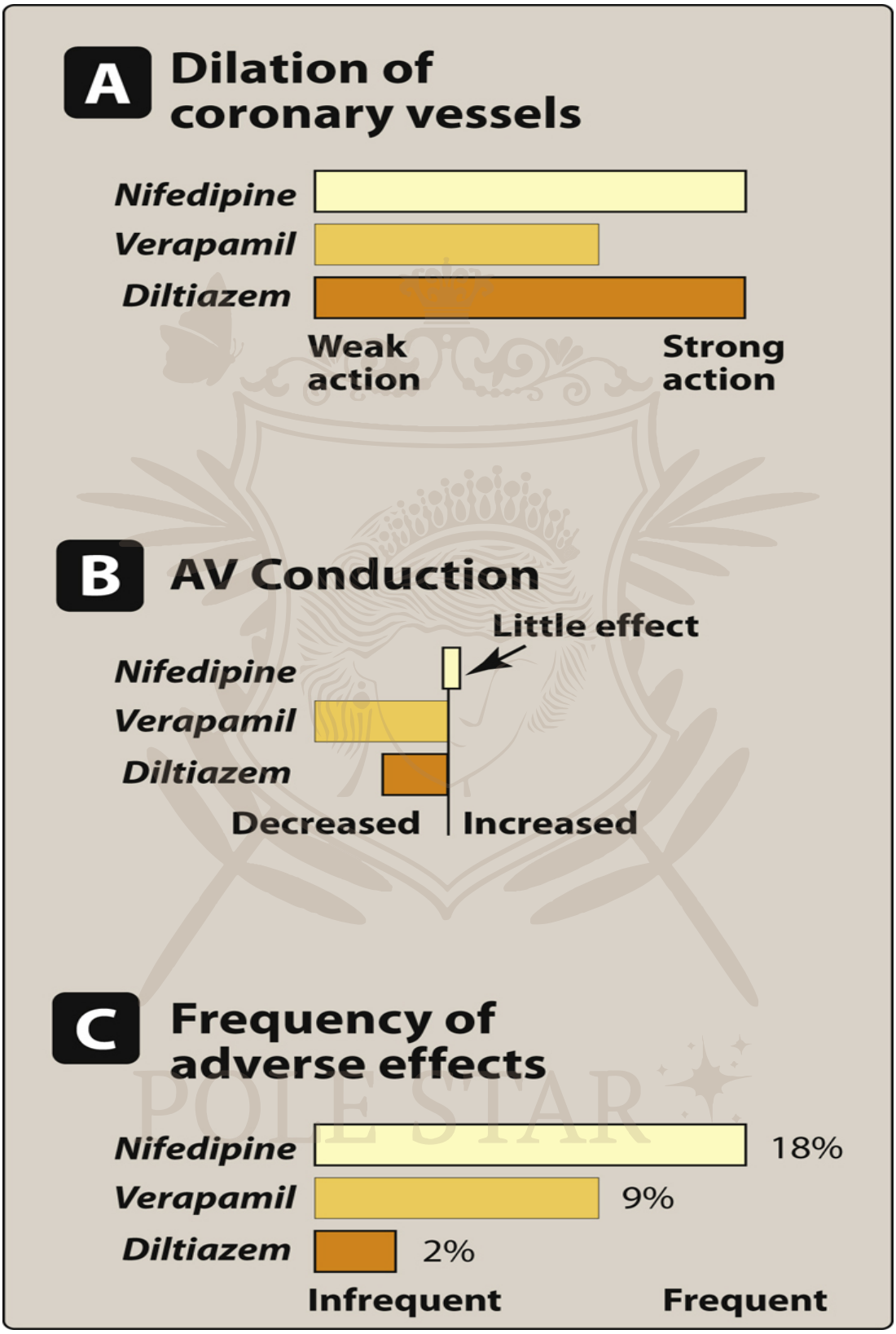

Figure 8.12 Actions of calcium channel blockers.AV = atrioventricular.

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1.Diphenylalkylamines: *Verapamil* [ver-AP-a-mil] is the only member of this class that is available in the United States. *Verapamil* slows cardiac conduction (negative dromotropy) and decreases heart rate (negative chronotropy) and contractility (negative inotropy). It is also used to treat angina and supraventricular tachyarrhythmias as well as to prevent migraine and cluster headaches.

2.Benzothiazepines: *Diltiazem* [dil-TYE-a-zem] is the only member of this class that is currently approved in the United States. *Diltiazem* affects both cardiac and vascular smooth muscle cells, but it has a less pronounced negative inotropic effect on the heart compared with that of *verapamil. Diltiazem* has a favorable side-effect profile.

3.Dihydropyridines: This class of calcium channel blockers includes *nifedipine* [nye-FED-i-peen] (the prototype), *amlodipine* [am-LOE-di-peen], *felodipine* [fe-LOE-di-peen], *isradipine* [is-RAD-i-peen], *nicardipine* [nye-KAR-di-peen], and *nisoldipine* [nye-ZOL-di-peen]. These agents differ in pharmacokinetics, approved uses, and drug interactions. All dihydropyridines have a much greater affinity for vascular calcium channels than for cardiac calcium channels. They are, therefore, particularly beneficial in treating hypertension. Dihydropyridines have minimal effects on cardiac conduction and heart rate.

B. Actions

The intracellular concentration of calcium plays an important role in maintaining the tone of smooth muscle and in the contraction (inotropy) of the myocardium. Calcium channel antagonists block the inward movement of calcium by binding to calcium channels in the heart and in smooth muscle of the coronary and peripheral arteriolar vasculature. This causes vascular smooth muscle to relax, dilating mainly arterioles. Calcium channel blockers do not dilate veins. For *diltiazem* and *verapamil*, the decreased conduction (negative dromotropy) of the heart's electrical system that results from altering calcium cell entry also decreases the heart rate (negative chronotropy).

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C. Therapeutic uses

In the management of hypertension, CCBs may be used as an initial therapy or as add-on therapy. They are useful in the treatment of hypertensive patients who also have asthma, diabetes, and/or peripheral vascular disease, because unlike β-blockers, they do not have the potential to adversely affect these conditions. All CCBs are useful in the treatment of angina. In addition, *diltiazem* and *verapamil* are used in the treatment of atrial fibrillation, where they reduce the risk of a rapid ventricular response.

D. Pharmacokinetics

Most of these agents have short half-lives (3-8 hours) following an oral dose. Sustained-release preparations are available and permit once-daily dosing. *Amlodipine* has a long half-life (30-50 hours) and does not require a sustained-release formulation.

E. Adverse effects

First-degree atrioventricular block and constipation are common dose-dependent side effects of *verapamil.* Because of their negative inotropic and dromotropic effects *verapamil* and *diltiazem* should be avoided in patients with atrioventricular block or heart failure with reduced ejection fraction. Dizziness, headache, and a feeling of fatigue caused by a decrease in blood pressure are more frequent adverse effects with the dihydropyridine agents (Figure 8.13). Peripheral edema is another commonly reported side effect of this class. *Nifedipine* and other dihydropyridines may cause gingival hyperplasia.

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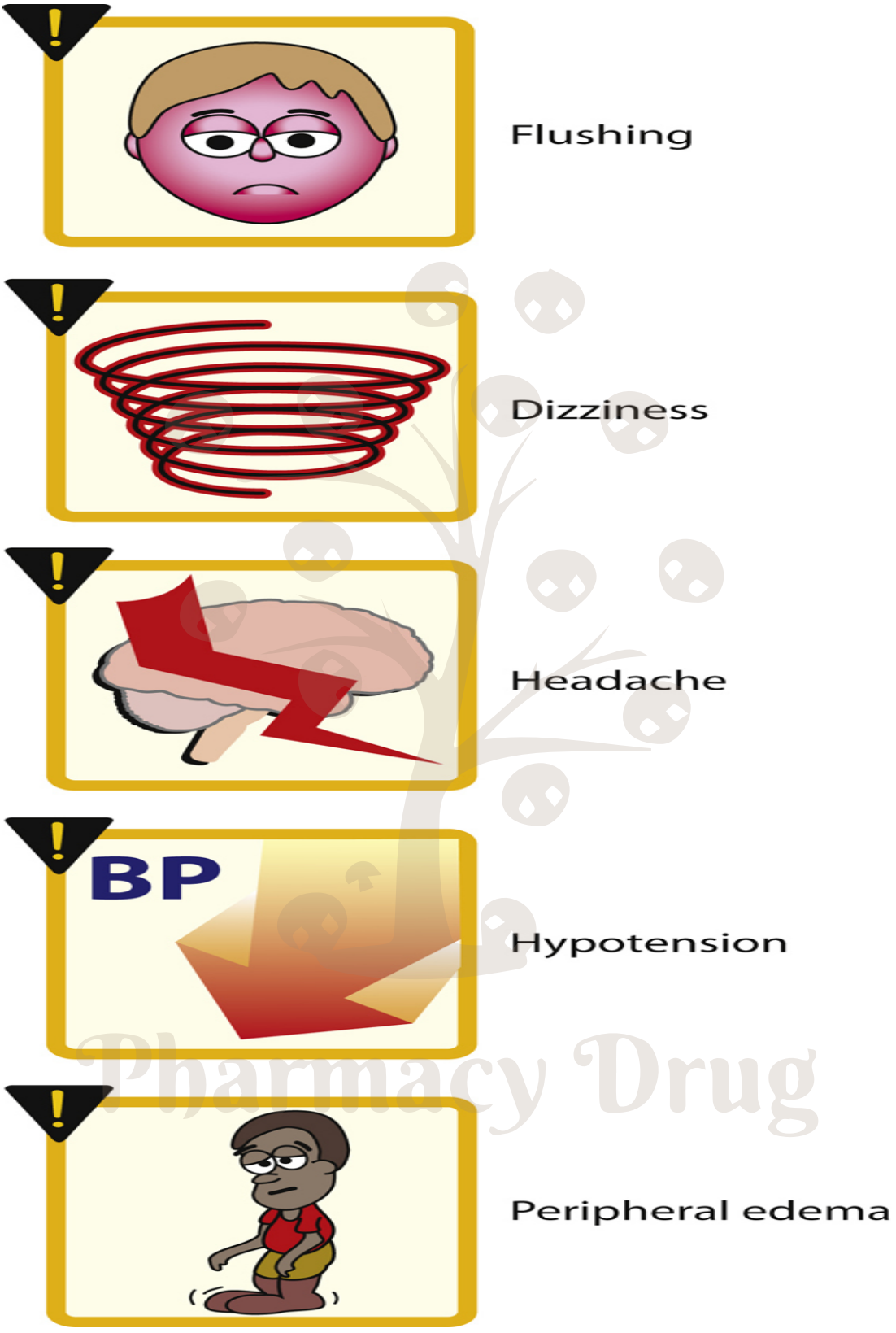

Figure 8.13 Some common adverse effects of the calcium channel blockers.

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XI. A-ADRENOCEPTOR–BLOCKING AGENTS

α-Adrenergic blockers used in the treatment of hypertension include *prazosin* [PRA-zoe-sin], *doxazosin* [dox-AY-zoe-sin], and *terazosin* [ter-AY-zoe-sin]. These agents produce a competitive blockade of α_1-adrenoceptors. They decrease peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial and venous smooth muscle. These drugs cause only minimal changes in cardiac output, renal blood flow, and glomerular filtration rate. Therefore, long-term tachycardia does not occur, but salt and water retention does. Reflex tachycardia and postural hypotension often occur at the onset of treatment and with dose increases, requiring slow titration of the drug. Unlike first-line antihypertensives, α-blockers have not demonstrated a positive impact on cardiovascular complications of hypertension, such as heart failure. As a result, α-blockers are no longer recommended as initial treatment for hypertension but may be used for cases of resistant hypertension. Other α_1-blockers that have greater selectivity for the prostate α-receptors are used in the treatment of benign prostatic hyperplasia (see Chapter 43).

XII. A-/B-ADRENOCEPTOR–BLOCKING AGENTS

Labetalol [la-BAY-ta-lol] and *carvedilol* [kar-VE-di-lol] block α_1, β_1, and β_2 receptors. *Carvedilol* is indicated in the treatment of heart failure and hypertension. It has been shown to reduce morbidity and mortality associated with heart failure. *Labetalol* is used in the management of gestational hypertension and hypertensive emergencies.

XIII. CENTRALLY ACTING ADRENERGIC DRUGS

@pharmacy_drug2

A. Clonidine

Clonidine [KLON-i-deen] acts centrally as an α_2 agonist to produce inhibition of sympathetic vasomotor centers, which decreases sympathetic outflow to the periphery. This leads to reduced total peripheral resistance and decreased blood pressure. *Clonidine* is used primarily for the treatment of hypertension that has not responded adequately to treatment with two or more drugs. *Clonidine* does not decrease renal blood flow or glomerular filtration and, therefore, is useful in the treatment of hypertension complicated by renal disease. *Clonidine* is well absorbed after oral administration and is excreted by the kidney. It is also available in a transdermal patch. Adverse effects include sedation, dry mouth, and constipation (Figure 8.14). Rebound hypertension occurs following abrupt withdrawal of *clonidine.* The drug should, therefore, be withdrawn slowly if discontinuation is required.

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Figure 8.14 Some adverse effects of *clonidine*.

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B. Methyldopa

Methyldopa [meth-ill-DOE-pa] is an α_2 agonist that is converted to methylnorepinephrine centrally to diminish adrenergic outflow from the CNS. The most common side effects of *methyldopa* are sedation and drowsiness. Its use is limited due to adverse effects and the need for multiple daily doses. It is mainly used for management of hypertension in pregnancy, where it has a long record of safety.

XIV. VASODILATORS

The direct-acting smooth muscle relaxants, such as *hydralazine* [hye-DRAL-a-zeen] and *minoxidil* [min-OX-i-dill], are usually reserved for resistant cases of hypertension. These vasodilators act by producing relaxation of vascular smooth muscle, primarily in arteries and arterioles. This results in decreased peripheral resistance and, therefore, blood pressure. Both agents produce reflex stimulation of the heart, resulting in the competing reflexes of increased myocardial contractility, heart rate, and oxygen consumption. These actions may prompt angina pectoris, myocardial infarction, or cardiac failure in predisposed individuals. [Note: In cases of severe hypertension accompanied by bradycardia, *hydralazine* is an appropriate agent.] Vasodilators also increase plasma renin concentration, resulting in sodium and water retention. These undesirable side effects can be mitigated by introduction of the agents at a low dose with slow titration, and/or concomitant use of a diuretic (to decrease sodium retention) and a β-blocker (to balance the reflex tachycardia). Together, the three drugs decrease cardiac output, plasma volume, and peripheral vascular resistance. *Hydralazine* is an approved therapy for controlling blood pressure in pregnancy-induced hypertension. Adverse effects of *hydralazine* include headache, tachycardia, nausea, sweating, arrhythmia, and precipitation of angina (Figure 8.15). A lupus-like syndrome can occur with high dosages, but it is reversible upon discontinuation of the drug. *Minoxidil* treatment causes hypertrichosis (the growth of body hair). This drug is used topically to treat male-pattern baldness.

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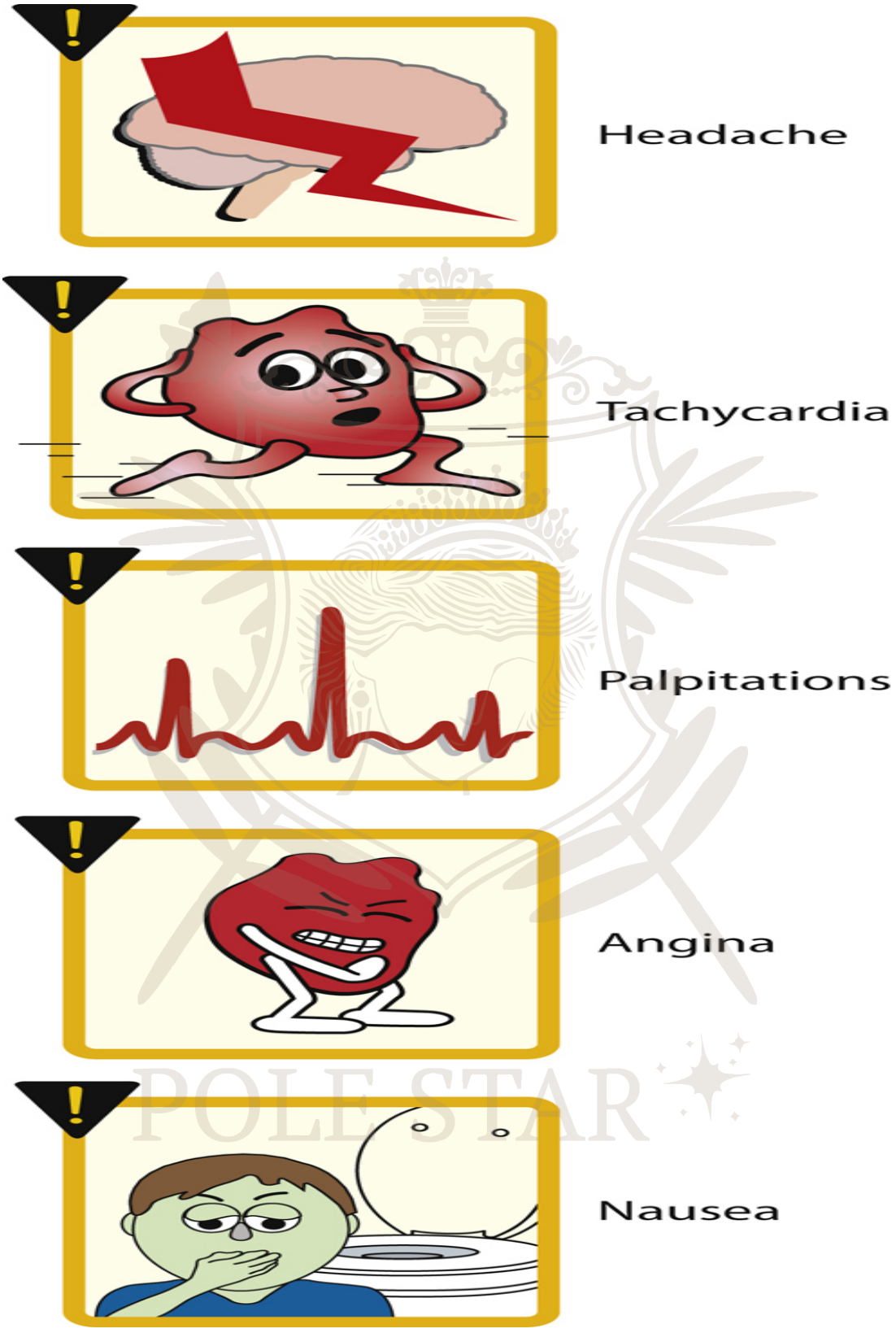

Figure 8.15 Some adverse effects of *hydralazine*.

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XV. HYPERTENSIVE EMERGENCY

Hypertensive emergency is a rare but life-threatening situation characterized by severe elevations in blood pressure (systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 120 mm Hg) with evidence of impending or progressive target organ damage (for example, stroke, myocardial infarction). [Note: A severe elevation in blood pressure without evidence of target organ damage is considered a hypertensive urgency.] Hypertensive emergencies require timely blood pressure reduction with treatment administered intravenously to prevent or limit target organ damage. A variety of medications are used, including calcium channel blockers (*nicardipine* and *clevidipine*), nitric oxide vasodilators (*nitroprusside* and *nitroglycerin*), adrenergic receptor antagonists (*phentolamine*, *esmolol*, and *labetalol*), the vasodilator *hydralazine*, and the dopamine agonist *fenoldopam.* Treatment is directed by the type of target organ damage and/or comorbidities present.

Clinical Application 8.3: Hypertensive Emergency

Determining if significantly elevated blood pressure (systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 120 mm Hg) is urgent or emergent often involves evidence of impending or progressive target organ damage (TOD). Examples of TOD include left ventricular hypertrophy, albuminuria, impaired renal function, unstable angina, and acute myocardial infarction. Hypertension transitions from urgent to emergent when organs such as the heart, brain, and kidney show signs of TOD, leading to immediate care at a hospital. Intravenous administration of antihypertensives allows for an appropriate rate of reduction in blood pressure, while also preventing and limiting TOD. The initial goal in hypertensive emergency is to reduce mean arterial pressure by no more than 25% within minutes to hours. Parenteral medications such as *enalaprilat*, *nicardipine*, and *labetalol* are examples of treatment for emergency situations.

XVI. RESISTANT HYPERTENSION

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Resistant hypertension is defined as blood pressure that remains elevated (above goal pressure) despite administration of an optimal three-drug regimen that includes a diuretic. The most common causes of resistant hypertension are poor compliance, excessive ethanol intake, concomitant conditions (diabetes, obesity, sleep apnea, hyperaldosteronism, high salt intake, and/or metabolic syndrome), concomitant medications (sympathomimetics, nonsteroidal anti-inflammatory drugs, or corticosteroids), insufficient dose and/or drugs, and use of drugs with similar mechanisms of action.

Chapter Summary

- Hypertension is diagnosed when systolic blood pressure exceeds 130 mm Hg or diastolic blood pressure exceeds 80 mm Hg.
- Arterial blood pressure is directly proportional to cardiac output and peripheral vascular resistance. Most antihypertensive drugs work by reducing cardiac output and/or decreasing peripheral vascular resistance via effects on the-autonomic nervous system or renin–angiotensin–aldosterone system.
- Hypertension often coexists with other conditions that can be aggravated by some of the antihypertensive drugs or that may benefit from their use, independent of blood pressure control. Designing antihypertensive regimens for a particular patient is important for improved clinical outcomes and avoidance of potential adverse effects.
- The treatment goal for hypertension in most individuals is a blood pressure of less than 130/80 mm Hg.
- The choice of initial drug therapy varies depending on the guideline and concomitant disease states. However, most patients can be treated with one of the four preferred drug classes: ACE inhibitors, ARBs, calcium channel blockers, or thiazide diuretics.
- Blood pressure is often inadequately controlled after initial therapy, and addition of a second agent is required. Selection of a second agent depends on minimizing adverse effects and providing the best regimen to achieve the desired blood pressure goal. Coexisting disease states should be considered.
- Thiazide diuretics decrease peripheral vascular resistance to improve blood pressure control. Thiazide diuretics are very useful in combination with other antihypertensives, but these agents lose efficacy in patients with an estimated glomerular filtration rate less than 30 mL/min/m^2.
- ACE inhibitors reduce peripheral vascular resistance by blocking the enzyme ACE, thereby reducing production of the potent vasoconstrictor angiotensin II and leading to vasodilation of both arterioles and veins. ACE inhibitors decrease workload of the heart and slow the progression of diabetic nephropathy. These agents are first-line therapy in patients with a history of diabetes, stroke, heart failure, myocardial infarction, or chronic kidney disease.

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- ARBs have a pharmacological and adverse-effect profile similar to that of ACE inhibitors. These agents lower blood pressure by working on the renin–angiotensin–aldosterone system. Unlike ACE inhibitors, they do not increase bradykinin levels. Therefore, patients are at lower risk of developing a cough or angioedema as compared with ACE inhibitors.
- Calcium channel blockers are divided into three chemical classes: diphenylalkylamines *(verapamil),* benzothiazepines (*diltiazem*), and dihydropyridines (*amlodipine, nifedipine*, etc.). The dihydropyridines have greater affinity for peripheral vascular calcium channels. This is particularly beneficial in treating hypertension, as compared with other classes of calcium channel blockers that work primarily on cardiac receptors.
- β-Blockers reduce blood pressure by decreasing cardiac output (negative inotropic and chronotropic activity). Although no longer considered first line, the class is useful in hypertensive patients with concomitant heart disease and chronic heart failure. Abrupt withdrawal can lead to severe hypertension, angina, myocardial infarction, and even sudden death in patients with ischemic heart disease. These agents should be tapered upon discontinuation.

STUDY QUESTIONS

Choose the ONE best answer.

8.1 A 60-year-old non-Hispanic white man has hypertension. His past medical history also includes asthma, diabetes, and hyperlipidemia. According to the ACC/AHA guidelines, which represents the most appropriate blood pressure goal for the patient?

A. Less than 140/80
B. Less than 135/85
C. Less than 120/85
D. Less than 130/80

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Correct answer = D. Goals of therapy differ depending on which guidelines the clinician uses in practice. According to the ACC/AHA guidelines the goal blood pressure for patients is less than 130/80.

8.2 A 62-year-old non-Hispanic Black man presents for treatment of hypertension. His past medical history also includes diabetes, depression, and hypertension. The blood pressure is 152/96 (both

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today and at the last visit). Which is a recommended initial therapy to treat hypertension in this patient?

A. Lisinopril
B. Clonidine
C. Diltiazem
D. Propranolol

Correct answer = A. Lisinopril is an ACE inhibitor and is recommended for first-line therapy in various patient populations, including those who have a compelling indication such as diabetes. The other therapies are not considered first-line therapy.

8.3 A patient was recently admitted to the hospital for angioedema. The home blood pressure medications included nifedipine, enalapril, prazosin, and metoprolol. Which home medication most likely caused the rare side effect of angioedema and should not be restarted?

A. Nifedipine
B. Enalapril
C. Prazosin
D. Metoprolol

Correct answer = B. ACE inhibitors (enalapril), ARBs (for example, losartan), and renin inhibitors (aliskiren) can cause angioedema. The occurrence of angioedema is more common with ACE inhibitors. Nifedipine can cause dizziness, headache, and peripheral edema. Prazosin can cause reflex tachycardia and postural hypotension. Metoprolol can cause insomnia, fatigue, and bradycardia.

8.4 The blood pressure of a patient with essential hypertension is at goal on treatment with ramipril. Since initiation of ramipril, the serum creatinine has increased 25% above baseline. What is the appropriate next step for the ramipril therapy?

A. Discontinue ramipril.
B. Reduce dose of ramipril.
C. Continue current dose of ramipril.
D. Increase dose of ramipril.

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Correct answer = C. The blood pressure is at goal. Electrolytes (such as potassium) and serum creatinine should be monitored in patients who initiate ACE inhibitors. Increases in serum creatinine up to 30% above baseline are acceptable and do not warrant discontinuation or reduction of treatment. Since the blood pressure is at goal, increasing the ramipril is not necessary.

8.5 Which of the following correctly outlines a major difference in electrolyte disturbances associated with thiazide and loop diuretics?

A. Thiazide diuretics decrease potassium and loop diuretics increase potassium.
B. Thiazide diuretics increase potassium and loop diuretics decrease potassium.
C. Thiazide diuretics decrease calcium and loop diuretics increase calcium.
D. Thiazide diuretics increase calcium and loop diuretics decrease calcium.

Correct answer = D. Thiazide and loop diuretics decrease potassium, sodium, and magnesium. However, thiazide diuretics increase calcium (through reduced urinary excretion), while loop diuretics reduce calcium (through enhanced urinary excretion).

8.6 A 45-year-old man was started on therapy for hypertension and developed a persistent, dry cough. His medication regimen consists of nifedipine, metoprolol, lisinopril, chlorthalidone, aspirin, metformin, and duloxetine. Which agent is most likely responsible for this side effect?

A. Lisinopril
B. Chlorthalidone
C. Nifedipine
D. Metoprolol

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Correct answer = A. The cough is most likely an adverse effect of the ACE inhibitor lisinopril. Chlorthalidone, nifedipine, and metoprolol do not cause this side effect.

8.7 A 63-year-old man presents for a blood pressure check. The blood pressure is 140/85 mm Hg, which is the same as the

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previous visit 6 weeks ago. The past medical history includes diabetes and stroke. The patient reports adherence with lifestyle modifications. Based on the information provided, which agent would be a reasonable option for management of the hypertension?

A. Lisinopril
B. Metoprolol
C. Furosemide
D. Spironolactone

Correct answer = A. Since the patient has diabetes and a history of stroke, three drug classes would be recommended to use in this scenario: ACE inhibitors, ARBs, or diuretics. The only medication that belongs to one of these classes is lisinopril.

8.8 A patient presents to the clinic after recent hospital visit for myocardial infarction. The blood pressure is 145/85 mm Hg. The current regimen consists of lisinopril (maximum effective dose), aspirin, clopidogrel, and amlodipine (maximum effective dose). What is the most appropriate agent to add to the regimen to achieve a goal blood pressure of 130/80 mm Hg?

A. Metoprolol
B. Valsartan
C. Nifedipine
D. Chlorthalidone

Correct answer = A. β-Blockers (metoprolol) are appropriate for a patient with previous myocardial infarction who is not at goal blood pressure. ARBs (valsartan) are not recommended in combination with ACE inhibitors (lisinopril). Nifedipine is in the same drug class as amlodipine (dihydropyridine calcium channel blocker). Thiazide diuretics are an option once the β-blocker dose is maximized.

8.9 A 75-year-old man reports to his primary care office feeling fatigued and weak. Upon examination the patient has bradycardia and a blood pressure of 110/60 mm Hg. The current antihypertensive regimen includes metoprolol, enalapril, amlodipine, and chlorthalidone. Which of his medications is contributing to his lower heart rate?

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A. Metoprolol
B. Enalapril
C. Chlorthalidone
D. Amlodipine

Correct answer = A. β-Blockers can lower heart rate. Considering the risk in this particular patient, the best recommendation would be to reduce the dose of the metoprolol or taper the drug to discontinue.

8.10 A patient was started on chlorthalidone for initial treatment of blood pressure and titrated up to a maximum effective dose. The blood pressure is still above goal. What type of information would be helpful when considering a second agent to reach the blood pressure goal?

A. Weight and height
B. Family history
C. Employment
D. Concomitant disease states

Correct answer = D. Hypertension often coexists with other conditions that can be aggravated by some of the antihypertensive drugs or that may benefit from their use independent of blood pressure. Matching antihypertensive drugs to a particular patient is important for improved clinical outcomes and avoidance of potential adverse effects.

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9

Diuretics

Zachary L. Cox

I. OVERVIEW

Diuretics are drugs that increase the volume of urine excreted. Most diuretic agents are inhibitors of renal ion transporters that decrease the reabsorption of Na^+ at different sites in the nephron. As a result, Na^+ is excreted in greater than normal amounts (natriuresis) along with other ions and water, which is carried passively to maintain osmotic equilibrium. Diuretics, thus, increase the volume of urine and often change its pH and the corresponding ionic composition of the urine and blood. The extent of the diuresis caused by different classes of diuretics varies considerably depending on the nephron segment in which they work. In addition to the ion transport inhibitors, other types of diuretics include osmotic diuretics, aldosterone antagonists, and carbonic anhydrase inhibitors. While diuretics are commonly used for management of excessive fluid retention (edema), many agents within this class are prescribed for nondiuretic indications or for the physiologic effects on the body resulting from their activity on the kidney. Examples, which are discussed below, include use of thiazides in hypertension, use of carbonic anhydrase inhibitors in glaucoma, and aldosterone antagonists used for heart failure. In this chapter, the diuretic drugs (Figure 9.1) are discussed in the order of their frequency of use.

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THIAZIDE DIURETICS

Chlorothiazide DIURIL
Chlorthalidone GENERIC ONLY
Hydrochlorothiazide (HCTZ) MICROZIDE
Indapamide GENERIC ONLY
Metolazone ZAROXOLYN

LOOP DIURETICS

Bumetanide BUMEX
Ethacrynic acid EDECRIN
Furosemide LASIX
Torsemide GENERIC ONLY

POTASSIUM-SPARING DIURETICS

Amiloride MIDAMOR
Eplerenone INSPRA
Spironolactone ALDACTONE
Triamterene DYRENIUM

CARBONIC ANHYDRASE INHIBITORS

Acetazolamide DIAMOX

OSMOTIC DIURETICS

Mannitol OSMITROL

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Figure 9.1 Summary of diuretic drugs.

II. NORMAL REGULATION OF FLUID AND ELECTROLYTES BY THE KIDNEYS

Approximately 16% to 20% of the blood entering the kidneys is filtered from the glomerular capillaries into Bowman's capsule. The filtrate, although normally free of proteins and blood cells, contains most of the low-molecular-weight plasma components in concentrations similar to that in the plasma. These include glucose, sodium bicarbonate, amino acids, and other organic solutes, as well as electrolytes, such as Na^+, K^+, and Cl^-. The kidney regulates the ionic composition and volume of urine by active reabsorption or secretion of ions and/or passive reabsorption of water at five segments along the nephron: (1) the proximal convoluted tubule, (2) the descending loop of Henle, (3) the ascending loop of Henle, (4) the distal convoluted tubule, and (5) the collecting tubule and duct (Figure 9.2).

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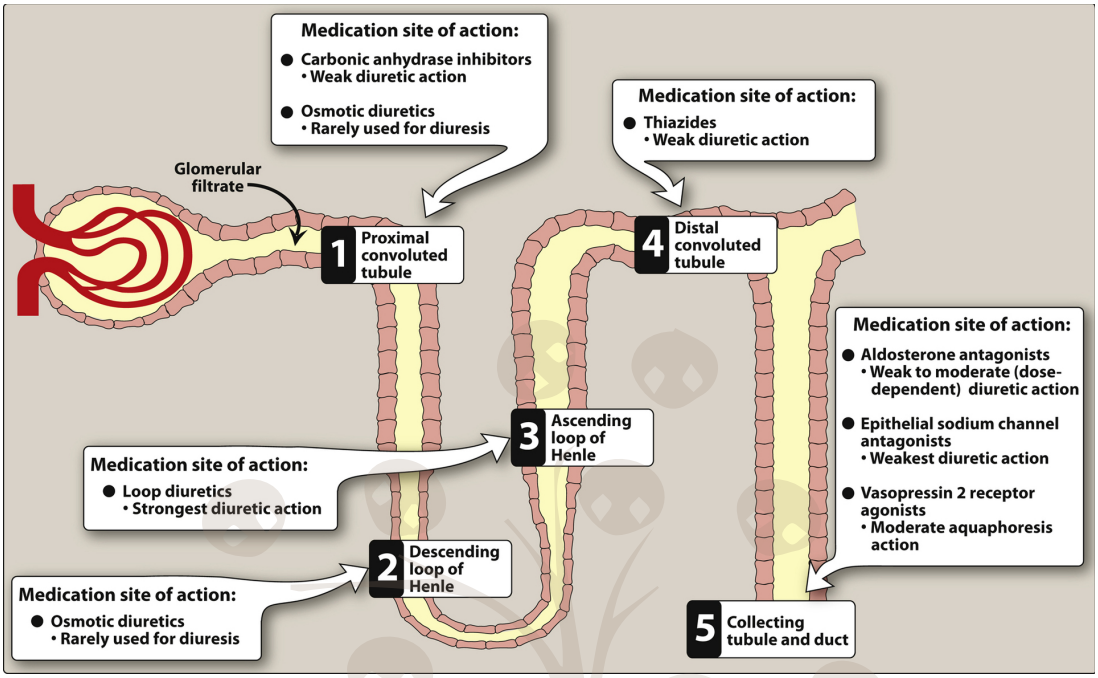

Figure 9.2 Major locations of ion and water exchange in the nephron, showing sites of action of the diuretic drugs.

A. Proximal convoluted tubule

The proximal convoluted tubule, located in the cortex of the kidney, reabsorbs almost all the glucose, bicarbonate, amino acids, and other solutes (Figure 9.3). Approximately 65% of the filtered Na^+ (and water) is reabsorbed. Na^+ is reabsorbed through the sodium–hydrogen exchanger (NHE3) in exchange for H^+ and through the sodium–glucose cotransporter-2. Although sodium–glucose cotransporter-2 inhibitors have diuretic action, their primary indications are nondiuretic related and include diabetes (see Chapter 24), heart failure (see Chapter 10), and chronic kidney disease. The Na^+ that is reabsorbed is pumped into the interstitium by the Na^+/K^+-adenosine triphosphatase (ATPase) pump. Given the high water permeability, about 60% of water is reabsorbed from the lumen to the blood to maintain osmolar equality. Chloride enters the lumen of the tubule in exchange for an anion, such as oxalate, as well as paracellularly through the lumen. Carbonic anhydrase in the luminal membrane and

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cytoplasm of the proximal tubular cells modulates the reabsorption of bicarbonate. Despite having the highest percentage of filtered Na^+ that is reabsorbed, diuretics working in the proximal convoluted tubule display weak diuretic properties. This weak activity results from the presence of a high-capacity Na^+ reabsorption area (loop of Henle) that is distal to the proximal convoluted tubule, which allows for reabsorption of any Na^+ remaining in the lumen and limits effective diuresis.

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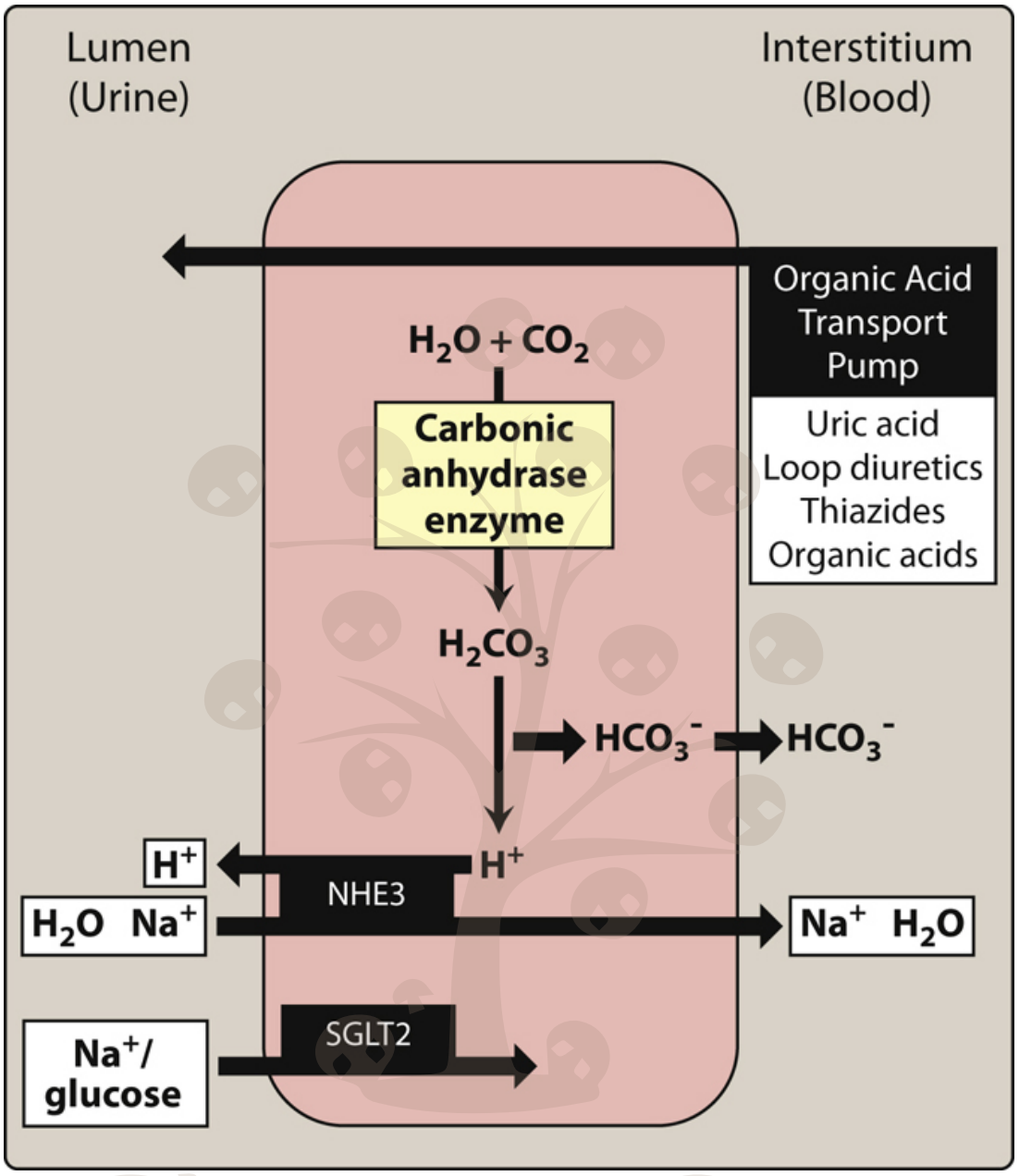

Figure 9.3 Proximal convoluted tubule cell.NHE3 = sodium-hydrogen exchanger; SGLT2 = sodium-glucose cotransporter-2.

The proximal tubule is the site of the organic acid and base secretory systems. The organic acid secretory system, located in the middle-third of the proximal tubule, secretes a variety of organic acids, such as uric acid, some antibiotics, and diuretics, from the bloodstream into the proximal tubular lumen. The organic

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acid secretory system is saturable, and diuretic drugs in the bloodstream compete for transfer with endogenous organic acids such as uric acid. A number of other interactions can also occur such as *probenecid*, which interferes with *penicillin* secretion. The organic base secretory system, located in the upper and middle segments of the proximal tubule, is responsible for the secretion of creatinine and choline.

B. Descending loop of henle

The remaining filtrate, which is isotonic, then enters the descending limb of the loop of Henle and passes into the medulla of the kidney. Water is reabsorbed due to the hypertonic interstitium of the medulla. The osmolarity of the filtrate increases along the descending portion of the loop of Henle because of the countercurrent mechanism that is responsible for water reabsorption. This results in a tubular fluid with a threefold increase in concentration of Na^+ and Cl^-. Osmotic diuretics exert part of their action in this region.

C. Ascending loop of henle

The cells of the ascending tubular epithelium are unique in being impermeable to water. Active reabsorption of Na^+, K^+, and Cl^- is mediated by a $Na^+/K^+/2Cl^-$ cotransporter (Figure 9.4). Both Mg^{2+} and Ca^{2+} are reabsorbed via the paracellular pathway. Thus, the ascending loop dilutes the tubular fluid and raises the osmolarity of the medullary interstitium, which drives water reabsorption at other segments of the nephron. Approximately 25% to 30% of the filtered sodium chloride is absorbed here. Because the ascending loop of Henle is a major site for salt reabsorption and no segments distally are capable of significant Na^+ or water reabsorption, drugs affecting this site (for example, loop diuretics) have the greatest diuretic effect.

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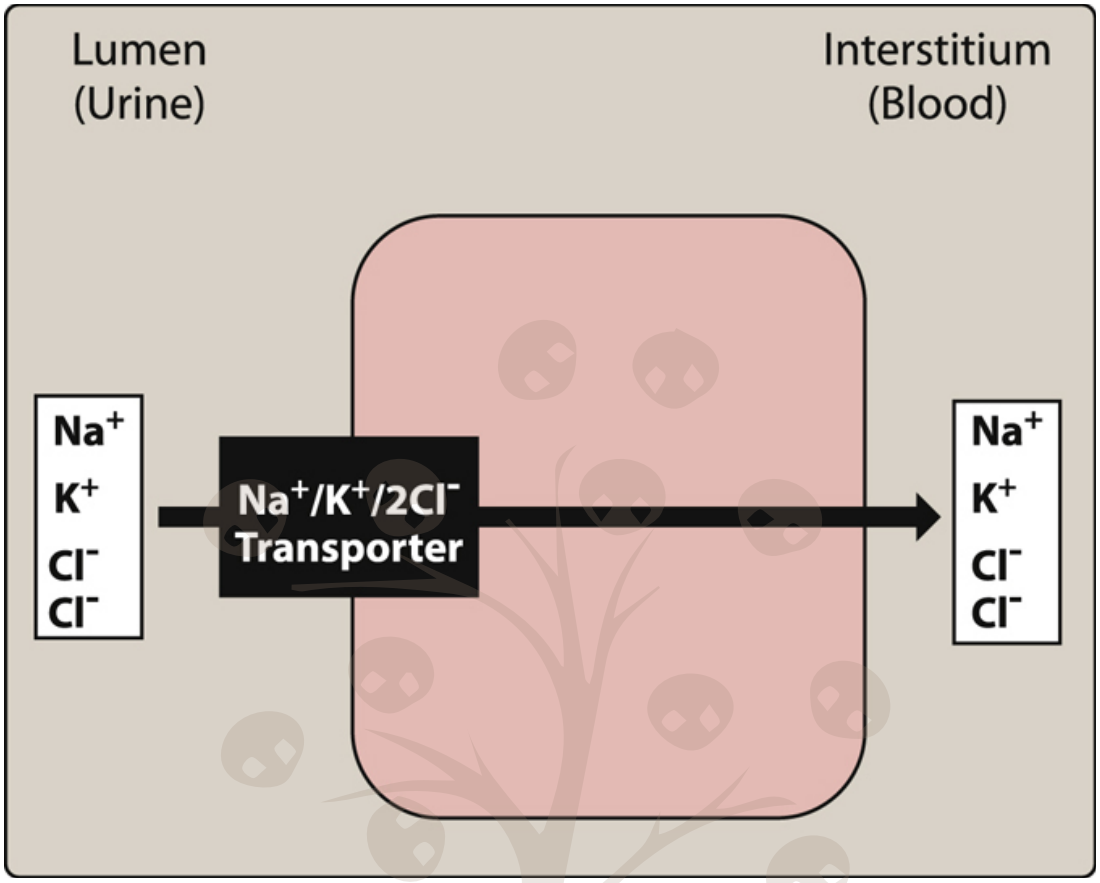

Figure 9.4 Ascending loop of Henle cell.

D. Distal convoluted tubule

The cells of the distal convoluted tubule are also impermeable to water. About 5% to 10% of the filtered sodium chloride is reabsorbed via a Na^+/Cl^- transporter, which is the target of thiazide diuretics. Under the regulation of parathyroid hormone, calcium reabsorption is mediated by an apical channel and then transported by a Na^+/Ca^{2+}-exchanger into the interstitial fluid (Figure 9.5).

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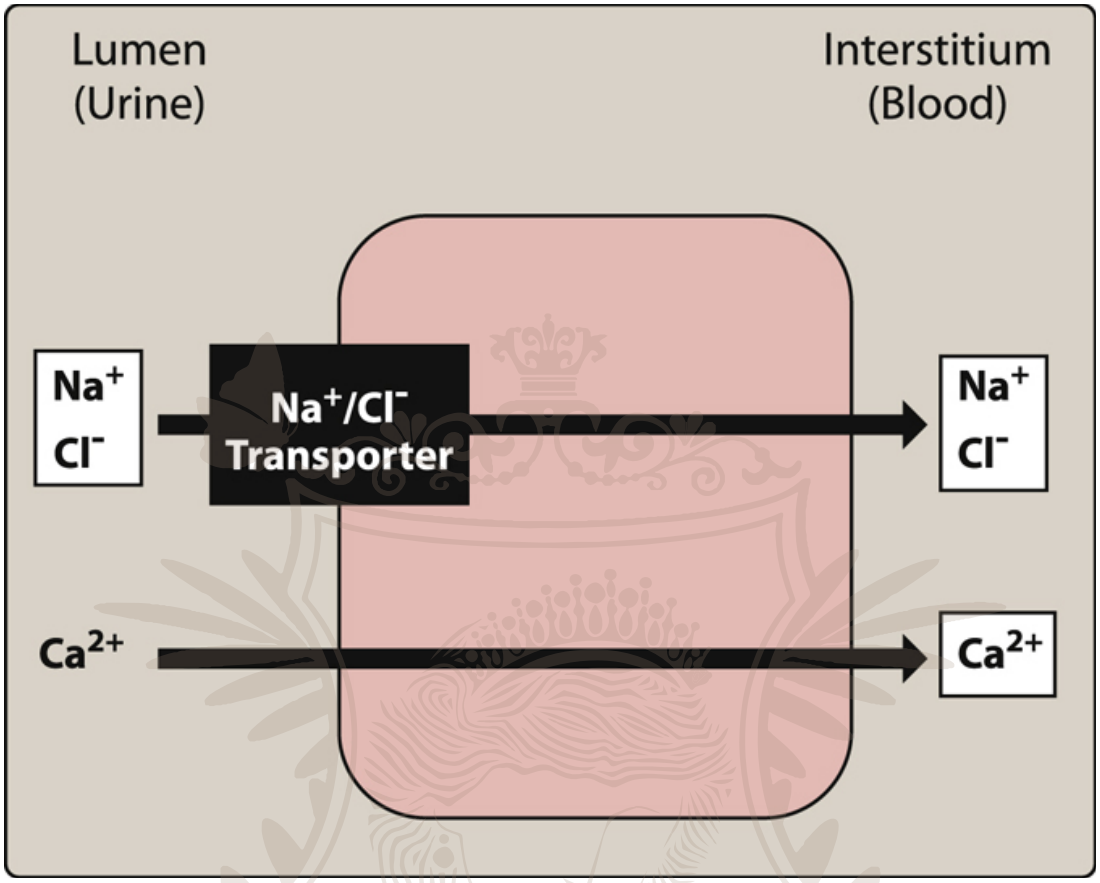

Figure 9.5 Distal convoluted tubule cell.

E. Collecting tubule and duct

The principal cells of the collecting tubule and duct are responsible for Na^+, K^+, and water transport, whereas the intercalated cells affect H^+ secretion (Figure 9.6). Approximately 1% to 2% of the filtered sodium enters the principal cells through epithelial sodium channels. These channels are inhibited by *amiloride* and *triamterene.* Once inside the cell, Na^+ reabsorption relies on a Na^+/K^+-ATPase pump to be transported into the blood. Aldosterone receptors in the principal cells influence Na^+ reabsorption and K^+ secretion. Aldosterone increases the synthesis of epithelial sodium channels and of the Na^+/K^+-ATPase pump to increase Na^+ reabsorption and K+ excretion. Antidiuretic

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hormone (ADH; vasopressin) binds to V2 receptors to promote the reabsorption of water through aquaporin channels.

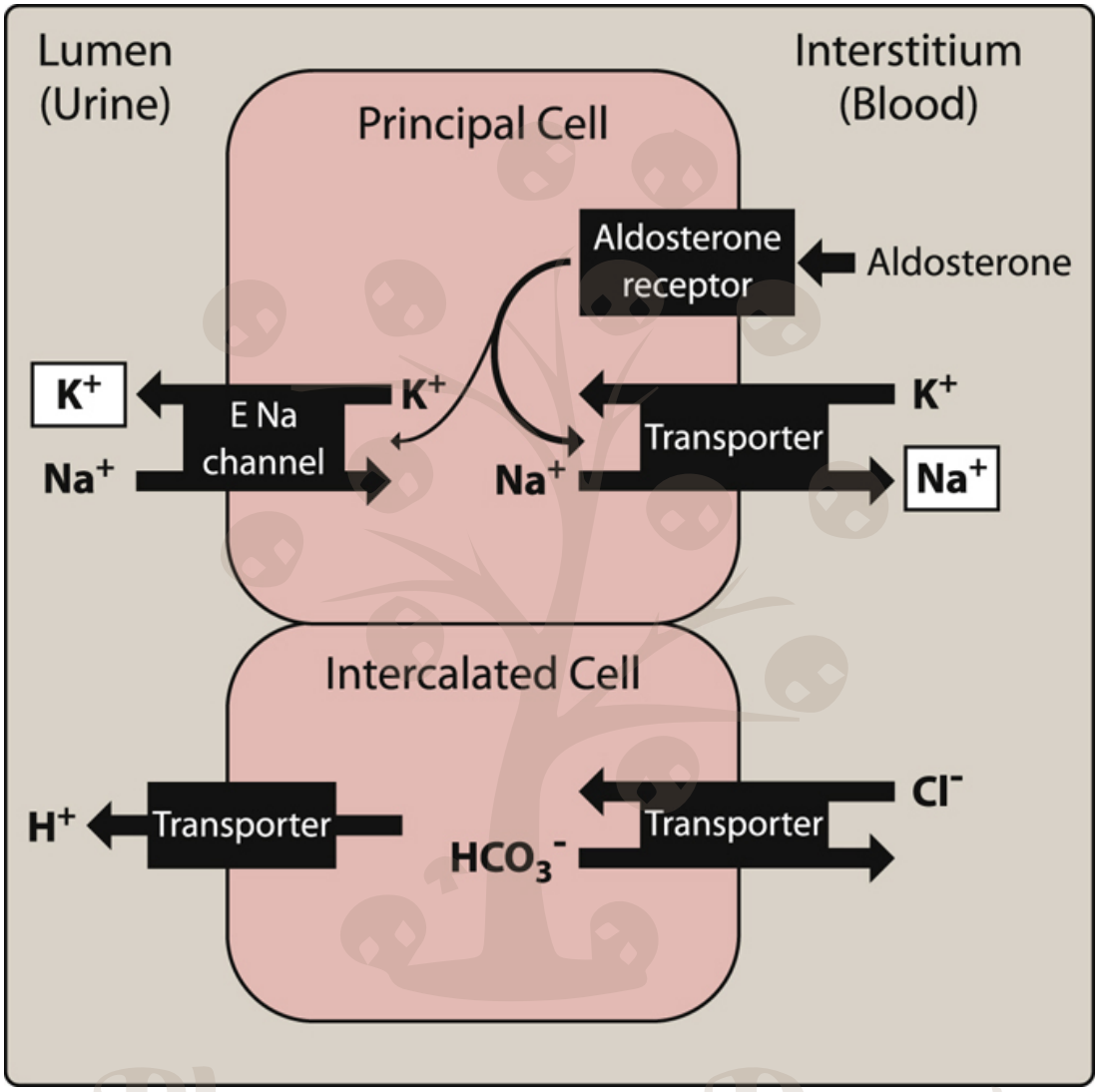

Figure 9.6 Collecting tubule and duct cells.E Na channel = epithelial sodium channel.

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III. THIAZIDES

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The thiazides are the most widely used diuretics because of their antihypertensive effects. However, the efficacy of thiazides for hypertension is not entirely dependent on their diuretic actions. These agents also reduce peripheral vascular resistance with long-term therapy. Despite being sulfonamide derivatives, thiazides do not generally cause hypersensitivity reactions in patients with allergies to sulfonamide antimicrobials such as *sulfamethoxazole.* All thiazides affect the distal convoluted tubule (Figure 9.2), and all have equal maximum diuretic effects, differing only in potency. Thiazides are sometimes called "low ceiling diuretics," because increasing the dose above normal therapeutic doses does not promote further diuretic response.

A. Thiazides and thiazide-like medications

Chlorothiazide [klor-oh-THYE-ah-zide] was the first orally active thiazide, although *hydrochlorothiazide* [hye-dro-klor-oh-THYE-ah-zide] and *chlorthalidone* [klor-THAL-i-done] are now used more commonly due to better bioavailability. *Hydrochlorothiazide* is more potent, so the required dose is considerably lower than that of *chlorothiazide*, but the efficacy is comparable with that of the parent drug. In all other aspects, *hydrochlorothiazide* resembles *chlorothiazide. Chlorthalidone* is approximately twice as potent as *hydrochlorothiazide. Chlorthalidone*, *indapamide* [in-DAP-a-mide], and *metolazone* [me-TOL-ah-zone] are referred to as thiazide-like diuretics because they lack the characteristic benzothiadiazine chemical structure; however, their mechanism of action, indications, and adverse effects are similar to those of *hydrochlorothiazide*.

1.Mechanism of action: The thiazide and thiazide-like diuretics act mainly in the distal convoluted tubule to decrease the reabsorption of Na^+ by inhibition of a Na^+/Cl^- cotransporter (Figure 9.5). As a result, these drugs increase the concentration of Na^+ and Cl^- in the tubular fluid. Thiazides must be excreted into the tubular lumen at the proximal convoluted tubule in order to be effective (Figure 9.3).

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Therefore, decreasing renal function reduces the diuretic effects. The antihypertensive effects of thiazides may persist even when the glomerular filtration rate is below 30 mL/min/1.73 m^2. However, hypertension at this level of renal dysfunction is often accompanied by hypervolemia, requiring a change to loop diuretics for management of volume status and corresponding blood pressure control. The efficacy of thiazides may be diminished with concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs), such as *indomethacin*, which inhibit production of renal prostaglandins and reduce renal blood flow.

2.Actions

a. Increased excretion of Na^+ and Cl^- Thiazide and thiazide-like diuretics cause diuresis with increased Na^+ and Cl^- excretion, which can result in the excretion of very hyperosmolar (concentrated) urine. This latter effect is unique, as the other diuretic classes are unlikely to produce a hyperosmolar urine. Figure 9.7 outlines relative changes in the ionic composition of the urine with thiazide and thiazide-like diuretics.

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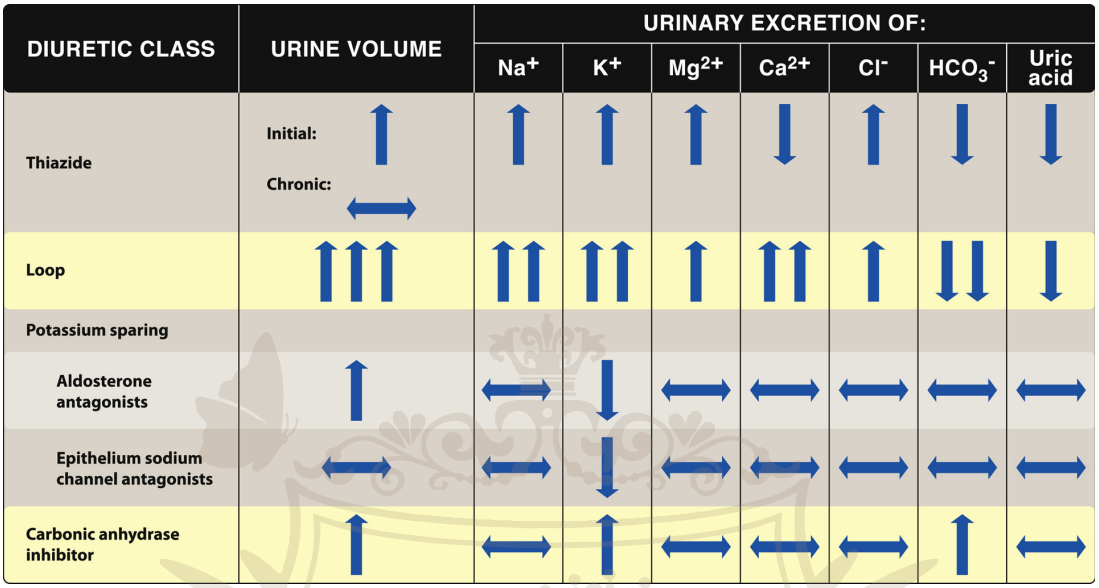

Figure 9.7 Urinary excretion from diuretic therapy.

b. Decreased urinary calcium excretion: Thiazide and thiazide-like diuretics decrease the Ca^{2+} content of urine by promoting the reabsorption of Ca^{2+} in the distal convoluted tubule where parathyroid hormone regulates reabsorption.

c. Reduced peripheral vascular resistance: An initial reduction in blood pressure results from a decrease in blood volume and, therefore, a decrease in cardiac output. With continued therapy, blood volume returns to baseline. However, antihypertensive effects continue, resulting from reduced peripheral vascular resistance caused by relaxation of arteriolar smooth muscle.

3. Therapeutic uses

a. Hypertension: Clinically, thiazides are a mainstay of antihypertensive treatment, because they are inexpensive, convenient to administer, and well tolerated. Blood pressure can be lowered with a daily dose of thiazide. At doses equipotent to *hydrochlorothiazide*,

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chlorthalidone is considered a preferred option by some clinicians because of its longer half-life (50-60 hours) and improved control of blood pressure over the entire day. However, current treatment guidelines for hypertension do not recommend any thiazide preferentially.

b. Heart failure: Loop diuretics (not thiazides) are the diuretics of choice in reducing extracellular volume in heart failure. However, thiazide diuretics may be added in patients resistant to loop diuretics, with careful monitoring for hypokalemia. *Metolazone* is most frequently utilized as an addition to loop diuretics, although there is a lack of evidence that it is more effective than other thiazides for this indication when administered at equipotent doses. Historically, thiazides were administered 30 minutes prior to loop diuretics to allow the thiazide time to reach the site of action when combined to augment diuresis in diuretic resistance. This practice is unnecessary and not supported by current evidence.

c. Hypercalciuria: The thiazides can be useful in treating idiopathic hypercalciuria and calcium oxalate stones in the urinary tract, because they inhibit urinary Ca^{2+} excretion.

d. Diabetes insipidus: Thiazides have the unique ability to produce a hyperosmolar urine. Thiazides can be utilized as a treatment for nephrogenic diabetes insipidus. The urine volume of such individuals may drop from 11 to about 3 L/d when treated with thiazides.

4.Pharmacokinetics: As a class, thiazides are effective orally, with a bioavailability of 60% to 70%. *Chlorothiazide* has a much lower bioavailability (15% to 30%) and is the only thiazide with an intravenous dosage form. Most thiazides take 1 to 3 weeks to produce a stable reduction in blood pressure and exhibit a prolonged half-life (approximately 10-15 hours).

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These agents are primarily excreted unchanged in the urine. *Indapamide* differs from the class because it undergoes hepatic metabolism and is excreted in both the urine and bile.

5.Adverse effects: These mainly involve problems in fluid and electrolyte balance (Figure 9.8).

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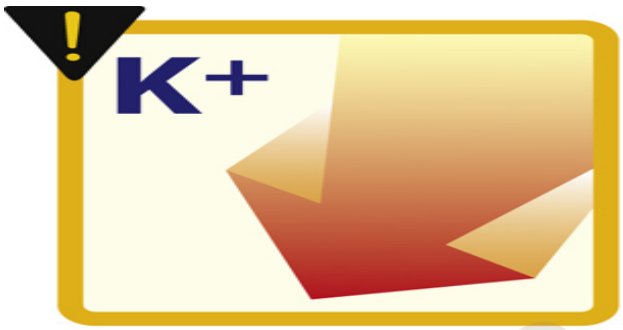

Hypokalemia

Hyperuricemia

Hypotension

Hyponatremia

Hypercalcemia

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Figure 9.8 Summary of adverse effects commonly observed with thiazide and thiazide-like medications.

a. Hypokalemia: Hypokalemia is the most frequent problem with the thiazide diuretics. Because thiazides increase Na^+ in the filtrate arriving at the distal tubule, more K^+ is also exchanged for Na^+, resulting in a continual loss of K^+ from the body with prolonged use of these drugs. Thus, serum K^+ should be measured periodically (more frequently at the beginning of therapy) to monitor for the development of hypokalemia. Potassium supplementation or combination with a potassium-sparing diuretic may be required. A low-sodium diet blunts the potassium depletion caused by thiazide diuretics.

b. Hypomagnesemia: Urinary loss of magnesium can lead to hypomagnesemia.

c. Hyponatremia: Hyponatremia may develop due to elevation of ADH, as well as diminished diluting capacity of the kidney and increased thirst.

d. Hyperuricemia: Thiazides increase serum uric acid by decreasing the amount of uric acid excreted through competition in the organic acid secretory system. Being insoluble, uric acid deposits in the joints and may precipitate a gouty attack in predisposed individuals. Therefore, thiazides should be used with caution in patients with gout or high levels of uric acid.

e. Hypovolemia: This can cause orthostatic hypotension or light-headedness.

f. Hypercalcemia: Thiazides inhibit the secretion of Ca^{2+}, sometimes leading to hypercalcemia (elevated levels of Ca^{2+} in the blood).

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g. Hyperglycemia: Therapy with thiazides can lead to mild elevations in serum glucose, possibly due to impaired release of insulin related to hypokalemia. Patients with diabetes still benefit from thiazide therapy but should monitor glucose to assess the need for an adjustment in diabetes therapy if thiazides are initiated.

IV. LOOP DIURETICS

Loop diuretics have their major diuretic action on the ascending limb of the loop of Henle (Figure 9.2). Of all the diuretics, these drugs have the highest efficacy in mobilizing Na^+ and Cl^- from the body, producing copious amounts of urine. Similar to thiazides, loop diuretics do not generally cause hypersensitivity reactions in patients with allergies to sulfonamide antimicrobials such as *sulfamethoxazole* because of structural differences in their sulfonamide derivative.

A. Loop diuretic medications

The loop diuretics include *bumetanide* [byoo-MET-ah-nide], *furosemide* [fur-OH-se-mide], *torsemide* [TOR-se-mide], and *ethacrynic* [eth-a-KRIN-ik] *acid. Furosemide* is the most commonly used of these drugs. The use of *bumetanide* and *torsemide* is increasing, as these agents have better bioavailability and are more potent compared with *furosemide. Ethacrynic acid* is used infrequently due to its adverse effect profile.

1.Mechanism of action: Loop diuretics inhibit the $Na^+/K^+/2Cl^-$ cotransporter located in the luminal membrane of the ascending limb of the loop of Henle (Figure 9.4). Therefore, reabsorption of these ions into the renal medulla is decreased. By lowering the osmotic pressure in the medulla, less water is reabsorbed from water-permeable segments, like the descending loop of Henle, causing diuresis. These agents

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have the greatest diuretic effect of all the diuretics because the ascending limb accounts for reabsorption of 25% to 30% of filtered NaCl and downstream sites are unable to compensate for the increased Na^+ load. Loop diuretics must be excreted into the tubular lumen at the proximal convoluted tubule to be effective (Figure 9.3). NSAIDs inhibit renal prostaglandin synthesis and can reduce the diuretic action of loop diuretics.

2.Actions

a. Diuresis: Loop diuretics cause diuresis, even in patients with poor renal function or lack of response to other diuretics. Changes in the composition of the urine induced by loop diuretics are shown in Figure 9.7.

Loop diuretics display a sigmoidal ("S"-shaped) dose–response curve with three parts: (1) a threshold effect, (2) a rapid increase in diuresis with small changes in drug concentration, and (3) a ceiling effect (Figure 9.9). A dose must be selected to cross the response threshold, which is patient specific. Reducing the effective dose with the intent of a reduction in diuresis can result in an absence of diuresis if the concentration of loop diuretic decreases below the response threshold. Likewise, increasing the effective dose may not cause more diuresis because of the ceiling effect. Thus, after determination of an effective diuretic dose, the clinician should modify the frequency of administration to increase or decrease the daily diuresis.

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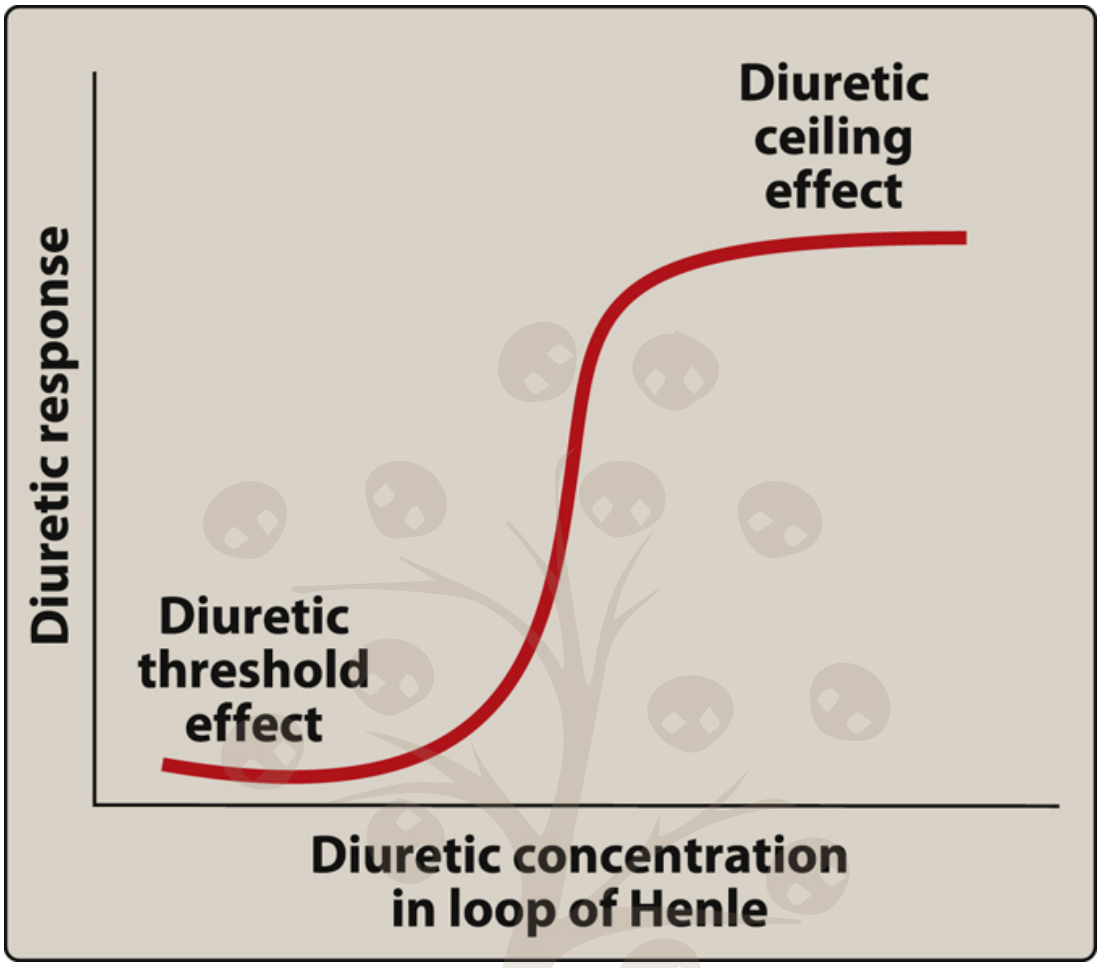

Figure 9.9 Loop diuretic dose–response curve.

Clinical Application 9.1: Dosing of Loop Diuretics

Dosing of loop diuretics is highly individualized due to the sigmoidal dose–response curve being shifted downward (lower maximal or ceiling effect) and to the right (greater diuretic concentration required to cross the diuretic threshold) in diuretic-resistant patients. One of the more difficult decisions is selection of the intravenous (IV) loop diuretic dose when a patient is admitted to the hospital for hypervolemia. The initial IV dose is best chosen as 2 to 2.5 times the chronic oral diuretic dose administered to that patient. For example, a patient on furosemide 40 mg orally twice daily would receive IV furosemide 100 mg twice daily. For patients who are diuretic naïve, IV furosemide 40 to 80 mg twice daily is a reasonable empiric dosing strategy. Subsequent doses should be titrated based on the diuretic response achieved with the initial dose. Diuretic response can be measured in amount of urine output, urine sodium excreted, or fluid

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weight lost. If urine output does not increase substantially within 2 hours of the dose of diuretic, an increased dose (typically double the prior dose) should be administered promptly. There is no need to wait until the next scheduled dose to make a dosage adjustment.

b. Increased urinary calcium excretion: Unlike thiazides, loop diuretics increase the Ca^{2+} content of urine. In patients with normal serum Ca^{2+} concentrations, hypocalcemia does not result, because Ca^{2+} is reabsorbed in the distal convoluted tubule.

c. Venodilation: Prior to their diuretic actions, loop diuretics cause acute venodilation and reduce left ventricular filling pressures via enhanced prostaglandin synthesis.

3. Therapeutic uses

a. Edema: Loop diuretics are the drugs of choice for treatment of pulmonary edema and acute/chronic peripheral edema caused from heart failure or renal impairment. Because of their rapid onset of action, particularly when given intravenously, the drugs are useful in emergency situations such as acute pulmonary edema.

b. Hypercalcemia: Loop diuretics (along with hydration) are also useful in treating hypercalcemia, because they stimulate tubular Ca^{2+} excretion.

c. Hyperkalemia: Loop diuretics can be used with or without replacement intravenous fluid for the treatment of hyperkalemia.

4. Pharmacokinetics: Loop diuretics are administered orally or parenterally. *Furosemide* has unpredictable bioavailability of 10% to 90% after oral administration. *Bumetanide* and *torsemide* have reliable bioavailability of 80% to 100%, which makes these agents preferred for oral therapy.

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The duration of action is approximately 6 hours for *furosemide* and *bumetanide*, and moderately longer for *torsemide*, allowing patients to predict the window of diuresis. [Note: The brand name for furosemide is Lasix, denoting that the duration of activity “lasts six” hours.]

5.Effects: Fluid and electrolyte issues are the predominant adverse effects (Figure 9.10).

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Ototoxicity

Hyperuricemia

Hypotension

Hypokalemia

Hypomagnesemia

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Figure 9.10 Summary of adverse effects commonly observed with loop diuretics.

a. Acute hypovolemia: Loop diuretics can cause a severe and rapid reduction in blood volume, with the possibility of hypotension, shock, and cardiac arrhythmias.

b. Hypokalemia: The heavy load of Na^+ presented to the collecting tubule results in increased exchange of tubular Na^+ for K^+, leading to hypokalemia, the most common adverse effect of the loop diuretics. The loss of K^+ from cells in exchange for H^+ leads to hypokalemic alkalosis. Use of potassium-sparing diuretics or supplementation with K^+ can prevent the development of hypokalemia.

c. Hypomagnesemia: Urinary loss of magnesium can lead to hypomagnesemia.

d. Ototoxicity: Reversible or permanent hearing loss may occur with loop diuretics, particularly when infused intravenously at fast rates, at high doses, or when used in conjunction with other ototoxic drugs (for example, aminoglycoside antibiotics). With current dosing and appropriate infusion rates, ototoxicity is a rare occurrence. *Ethacrynic acid* is the most likely to cause ototoxicity. Although less common, vestibular function may also be affected, inducing vertigo.

e. Hyperuricemia: Loop diuretics compete with uric acid for the renal secretory systems, thus blocking its secretion. These agents may cause or exacerbate gouty attacks.

f. Hyponatremia: Hyponatremia is less common than with thiazides and typically only occurs when combined

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with another disease process that lowers serum sodium or in the case of copious water ingestion.

V. POTASSIUM-SPARING DIURETICS

Potassium-sparing diuretics act in the collecting tubule to inhibit Na^+ reabsorption and K^+ excretion (Figure 9.6). Potassium levels must be monitored in patients treated with potassium-sparing diuretics. These drugs should be used cautiously in moderate renal dysfunction and avoided in patients with severe renal dysfunction because of the increased risk of hyperkalemia. Within this class, there are drugs with two distinct mechanisms of action and different indications for use: aldosterone antagonists and epithelial sodium channel blockers. Changes in the composition of the urine induced by potassium-sparing diuretics are shown in Figure 9.7.

A. Aldosterone antagonists

1. Mechanism of action: *Spironolactone* [spir-ON-oh-LAK-tone] and *eplerenone* [ep-LER-e none] are synthetic steroids that antagonize aldosterone receptors. This prevents translocation of the receptor complex into the nucleus of the target cell, ultimately resulting in a lack of intracellular proteins that stimulate the Na^+/K^+ exchange sites of the collecting tubule. Thus, aldosterone antagonists prevent Na^+ reabsorption and, therefore, K^+ and H^+ secretion. *Eplerenone* is more selective for aldosterone receptors and causes fewer endocrine effects (for example, gynecomastia) than *spironolactone*, which also binds to progesterone and androgen receptors.

Clinical Application 9.2: Aldosterone Antagonists

Aldosterone antagonists have diverse effects depending on the dosage used and the disease state treated. In heart failure with reduced ejection fraction, 25 to 50 mg once daily regimens of *spironolactone* or *eplerenone* reduce death and hospitalization without significant diuretic effect or blood pressure reduction. In

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resistant hypertension, the same daily doses produce a significant reduction in blood pressure. At daily doses of 100 mg or more, *spironolactone* and *eplerenone* produce clinically significant diuresis and are utilized for the treatment of cirrhotic ascites. Regardless of the disease state, the risk of hyperkalemia increases with the dose and with lower glomerular filtration rates (particularly less than 30 mL/min/1.73 m^2).

2.Actions: *Spironolactone* and *eplerenone* antagonize aldosterone receptors at renal sites, which causes diuresis, and nonrenal sites, which causes multiple hormonal effects. In most edematous states, blood levels of aldosterone are high, causing retention of Na^+. *Spironolactone* antagonizes the activity of aldosterone, resulting in retention of K^+ and excretion of Na^+.

3.Therapeutic uses

a. Edema: Aldosterone antagonists are particularly effective diuretics when used in high doses for edema associated with secondary hyperaldosteronism, such as hepatic cirrhosis and nephrotic syndrome. *Spironolactone* is the diuretic of choice in patients with hepatic cirrhosis with fluid in the peritoneal cavity (ascites). By contrast, in patients who have no significant circulating levels of aldosterone, there is minimal diuretic effect with use of this drug.

b. Hypokalemia: Although the aldosterone antagonists have a low efficacy in removing Na^+ from the body in comparison with the other diuretics, they have the secondary effect of causing the retention of K^+. Subsequently, these agents are often given in conjunction with thiazide or loop diuretics to offset the K^+ excretion that occurs with those diuretics.

c. Heart failure: Aldosterone antagonists are employed at lower doses to prevent unwanted myocardial remodeling mediated by aldosterone. Use of these agents

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has been shown to decrease mortality associated with heart failure, particularly in those with a reduced ejection fraction.

d. Resistant hypertension: Resistant hypertension, defined by the use of three or more medications without reaching the blood pressure goal, often responds well to aldosterone antagonists. This effect can be seen in those with or without elevated aldosterone levels.

e. Polycystic ovary syndrome: *Spironolactone* is often used off-label for the treatment of polycystic ovary syndrome. It blocks androgen receptors and inhibits steroid synthesis at high doses, thereby helping to offset increased androgen levels seen in this disorder.

4. Pharmacokinetics: Both *spironolactone* and *eplerenone* are well absorbed after oral administration. S*pironolactone* is extensively metabolized and converted to several active metabolites, which contribute to the therapeutic effects. *Eplerenone* is metabolized by cytochrome P450 3A4.

5. Adverse effects

a. Hyperkalemia: Hyperkalemia is the most common side effect. It is dose dependent and increases with renal dysfunction or use of other potassium-sparing agents such as angiotensin-converting enzyme inhibitors and potassium supplements.

b. Gynecomastia: *Spironolactone*, but not *eplerenone*, may induce gynecomastia in approximately 10% of men and instigate menstrual irregularities in women.

B. Triamterene and amiloride

Triamterene [trye-AM-ter-een] and *amiloride* [a-MIL-oh-ride] block epithelial sodium channels, resulting in a decrease in Na^+/K^+

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exchange. Although they have a K^+-sparing diuretic action similar to that of the aldosterone antagonists, their ability to block the Na^+/K^+ exchange site in the collecting tubule does not depend on the presence of aldosterone. Like the aldosterone antagonists, these agents are not very efficacious diuretics. Both *triamterene* and *amiloride* are commonly used in combination with other diuretics, almost solely for their potassium-sparing properties.

VI. CARBONIC ANHYDRASE INHIBITOR

Acetazolamide [ah-set-a-ZOLE-a-mide] and other carbonic anhydrase inhibitors are more often used for their other pharmacologic actions than for their diuretic effect, because they are much less efficacious than thiazides or loops for promoting diuresis.

A. Acetazolamide

1. Mechanism of action: *Acetazolamide* inhibits carbonic anhydrase located intracellularly (cytoplasm) and on the apical membrane of the proximal tubular epithelium (Figure 9.3). [Note: Carbonic anhydrase catalyzes the reaction of CO_2 and H_2O, leading to H_2CO_3, which spontaneously ionizes to H^+ and HCO_3^- (bicarbonate).] The decreased ability to exchange Na^+ for H^+ in the presence of *acetazolamide* results in a mild diuresis. Additionally, HCO_3^- is retained in the lumen, with marked elevation in urinary pH. The loss of HCO_3^- causes a hyperchloremic metabolic acidosis. Changes in the composition of urinary electrolytes induced by *acetazolamide* are summarized in Figure 9.7.

2. Therapeutic uses

a. Glaucoma: Oral *acetazolamide* decreases the production of aqueous humor and reduces intraocular

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pressure in patients with chronic open-angle glaucoma, probably by blocking carbonic anhydrase in the ciliary body of the eye. Topical carbonic anhydrase inhibitors, such as *dorzolamide* and *brinzolamide*, have the advantage of not causing systemic effects.

b. Altitude sickness: *Acetazolamide* can be used in the prophylaxis of symptoms of altitude sickness by creating a metabolic acidosis in order to mitigate a developing respiratory alkalosis from a decreased inhaled oxygen concentration. *Acetazolamide* prevents weakness, breathlessness, dizziness, nausea, and cerebral as well as pulmonary edema characteristic of the syndrome.

3. Pharmacokinetics: *Acetazolamide* can be administered orally or intravenously. It is approximately 90% protein bound and eliminated renally by both active tubular secretion and passive reabsorption.

4. Adverse effects: Metabolic acidosis (mild), potassium depletion, renal stone formation, drowsiness, and paresthesia may occur. The drug should be avoided in patients with hepatic cirrhosis, because it could lead to a decreased excretion of NH_4^+.

VII. OSMOTIC DIURETICS

A number of simple, hydrophilic chemical substances that are filtered through the glomerulus, such as *mannitol* [MAN-i-tol], result in diuresis (Figure 9.2). Filtered substances that undergo little or no reabsorption result in a higher osmolarity of the tubular fluid. This limits additional water reabsorption at the descending loop of Henle and proximal convoluted tubule, resulting in osmotic diuresis with little additional Na^+ excretion (aquaresis). Therefore, these agents are not useful for treating conditions in which Na^+ retention occurs. They are used to maintain urine flow following acute toxic ingestion

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of substances capable of producing acute renal failure. Osmotic diuretics are a mainstay of treatment for patients with increased intracranial pressure. [Note: *Mannitol* is not absorbed when given orally and should be given intravenously.] Adverse effects include dehydration and extracellular water expansion from the osmotic effects in the systemic circulation. The expansion of extracellular water occurs because the presence of *mannitol* in the extracellular fluid extracts water from the cells and causes hyponatremia until diuresis occurs.

Chapter Summary

- The various classes of diuretics work in different segments of the nephron, produce varying magnitudes of diuresis, contribute to different serum electrolyte changes, and have unique therapeutic indications outside of their diuretic action.
- Thiazide (and thiazide-like) diuretics work in the distal convoluted tubules; however, their mild, transient diuretic effect limits their use as monotherapy in the treatment of hypervolemia. The primary use of this class is to treat hypertension.
- Loop diuretics work in the ascending loop of Henle to produce the greatest magnitude of diuresis. This is the primary diuretic class used to treat conditions of hypervolemia.
- Two distinct medication classes, aldosterone antagonists and epithelial sodium channel antagonists, are classified as "potassium-sparing diuretics" but possess different mechanisms of action and therapeutic indications.
- Potassium sparing diuretics, which work in the collecting tubules and ducts, produce a weak diuretic effect and are coupled with other diuretic agents to mitigate their hypokalemic effect.
- Carbonic anhydrase inhibitors, such as *acetazolamide*, work in the proximal tubules of the nephron and are weak diuretics. This medication class is primarily utilized for nondiuretic indications.

STUDY QUESTIONS

Choose the ONE best answer.

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9.1 Which segment of the nephron reabsorbs the greatest amount of sodium and water?

A. Proximal tubules
B. Loop of Henle
C. Distal convoluted tubules
D. Collecting tubules and ducts

Correct answer = A. The proximal tubules reabsorb approximately 65% of the filtered sodium and filtrate in normal individuals.

9.2 Which diuretic has the ability to produce the greatest amount of urine?

A. Amiloride
B. Torsemide
C. Chlorothiazide
D. Acetazolamide

Correct answer = B. Loop diuretics have the ability to produce the largest diuresis. Although acetazolamide works in the proximal tubules where a greater amount of sodium and filtrate can be reabsorbed, it possesses a weak diuretic effect.

9.3 An elderly patient with a history of heart failure with preserved ejection fraction presents with dyspnea and radiographic imaging of the chest indicates pulmonary edema. The respiratory rate is 24 breaths per minute. Which treatment is indicated?

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A. Oral acetazolamide
B. Intravenous chlorothiazide
C. Intravenous furosemide
D. Oral spironolactone

Correct answer = C. It is important to administer a diuretic that reduces fluid accumulation in the lungs and improves oxygenation and heart function. The

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loop diuretics are most effective in removing large fluid volumes from the body and are the treatment of choice in this situation. In this situation, furosemide should be administered intravenously. The other choices are inappropriate, as they will not cause an acute diuresis with sufficient urine output to treat hypervolemia.

9.4 A group of college students is planning a mountain climbing trip to the Andes. Which of the following is most appropriate for them to take to prevent altitude sickness?

A. Thiazide diuretics such as hydrochlorothiazide
B. An anticholinergic such as atropine
C. A carbonic anhydrase inhibitor such as acetazolamide
D. A loop diuretic such as furosemide

Correct answer = C. Acetazolamide is used prophylactically for several days before an ascent above 10,000 ft. This treatment prevents the cerebral and pulmonary problems associated with altitude sickness as well as other difficulties, such as nausea.

9.5 A 51-year-old man has developed decompensated hepatic cirrhosis secondary to chronic alcoholism. He suffers from large-volume ascites and lower extremity edema. To control the ascites and edema, which of the following should be prescribed?

A. Amiloride
B. Chlorthalidone
C. Furosemide
D. Spironolactone

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Correct answer = D. Spironolactone at higher doses (100 mg daily or greater) is very effective in the treatment of edema and ascites from cirrhosis. These patients may also require combination of loop diuretics with spironolactone to control edema. While also categorized as a potassium sparing diuretic, amiloride does not antagonize aldosterone's effects and does not result in the same diuretic benefit.

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9.6 A 55-year-old man with calcium oxalate kidney stones needs a medication to decrease urinary calcium excretion, with the goal of reducing future kidney stones. Which diuretic is best for this indication?

A. Torsemide
B. Hydrochlorothiazide
C. Spironolactone
D. Triamterene

Correct answer = B. Hydrochlorothiazide is effective in increasing calcium reabsorption, thus decreasing the amount of calcium excreted, and decreasing the formation of kidney stones that contain calcium phosphate or calcium oxalate. Furosemide increases the excretion of calcium, whereas the K^+-sparing diuretics, spironolactone, and triamterene do not have an effect on calcium.

9.7 An 86-year-old patient with heart failure with preserved ejection fraction, hypertension, and chronic kidney disease is admitted to the hospital with hyperkalemia. The estimated glomerular filtration rate is 20 mL/min/1.73 m^2. The patient is taking bumetanide, valsartan/hydrochlorothiazide, carvedilol, and eplerenone. Which diuretic medication is most likely to be the cause of the hyperkalemia?

A. Bumetanide
B. Hydrochlorothiazide
C. Carvedilol
D. Eplerenone

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Correct answer = D. Eplerenone acts in the collecting tubule via aldosterone antagonism to inhibit Na^+ reabsorption and K^+ excretion. It is extremely important that patients who are treated with any potassium-sparing diuretic be closely monitored for potassium levels. Eplerenone is generally avoided when the glomerular filtration rate is below 30 mL/min/1.73 m^2 due to the risk of hyperkalemia. Bumetanide and hydrochlorothiazide promote the excretion of potassium, while carvedilol is not a diuretic and does not affect serum potassium concentrations.

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9.8 A 59-year-old man in the intensive care unit has a metabolic alkalosis. Which therapy will treat this condition?

A. Amiloride
B. Hydrochlorothiazide
C. Mannitol
D. Acetazolamide

Correct answer = D. Acetazolamide causes an increase in the urinary excretion of bicarbonate, lowering the pH of the blood.

9.9 A 49-year-old woman is following up in an ambulatory care clinic for resistant hypertension. Her blood pressure diary shows blood pressures consistently above goal. Her current medication regimen includes maximum doses of lisinopril, hydrochlorothiazide, and nifedipine. She is euvolemic by physical exam. What therapy is best to treat her resistant hypertension?

A. Change hydrochlorothiazide to indapamide
B. Add furosemide
C. Add chlorthalidone
D. Add spironolactone

Correct answer = D. Resistant hypertension, defined by the use of three or more medications without reaching the blood pressure goal, often responds well to aldosterone antagonists. This effect can be seen in those with or without elevated aldosterone levels. Changing to a different thiazide (indapamide) or adding another thiazide (chlorthalidone) is unlikely to be better than her current thiazide therapy. Furosemide is not indicated, as the patient is not hypervolemic and it will not result in arterial vasodilation.

9.10 An elderly woman is being treated in the hospital with IV furosemide for hypervolemia secondary to heart failure. She is failing to produce a urine output necessary to resolve her edema and only makes 500 mL of urine in the 6 hours following

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the dose. Which therapeutic change is best to increase her diuretic response?

A. Increase the frequency of furosemide to twice daily
B. Double the dose of the furosemide
C. Change furosemide to hydrochlorothiazide
D. Add metolazone to furosemide

Correct answer = B. The furosemide dose has not produced a diuretic concentration high enough to cross the “diuretic threshold.” Increasing the dose is the best method to increase the diuretic response. Changing to a thiazide will not result in more diuresis, as the loop of Henle reabsorbs a higher percentage of sodium than the distal tubules. Adding a thiazide such as metolazone would increase the diuretic response but will cause significant electrolyte abnormalities, such as profound hypokalemia. This should be reserved for when a diuretic response is not achieved with significantly higher loop diuretic doses.

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10

Drugs for Heart Failure

Shawn David Anderson, Katherine Vogel Anderson

I. OVERVIEW

Heart failure (HF) is a complex, progressive disorder in which the heart is unable to pump sufficient blood to meet the needs of the body. Its cardinal symptoms are dyspnea, fatigue, and fluid retention. HF is due to an impaired ability of the heart to adequately fill with and/or eject blood. It is often accompanied by abnormal increases in blood volume and interstitial fluid. Underlying causes of HF include, but are not limited to, atherosclerotic heart disease, diabetes mellitus, hypertensive heart disease, valvular heart disease, and congenital heart disease.

A. Role of pathophysiologic mechanisms in the progression of HF

Goals of treatment are to alleviate symptoms, slow disease progression, and improve survival. The following classes of drugs have been shown to be effective: (1) angiotensin-converting enzyme (ACE) inhibitors, (2) angiotensin receptor blockers, (3) angiotensin receptor–neprilysin inhibitors (ARNIs), (4) β-blockers, (5) diuretics, (6) hyperpolarization-activated cyclic nucleotide-gated channel blockers, (7) inotropic agents, (8) mineralocorticoid receptor antagonists, (9) sodium–glucose cotransporter 2 (SGLT2) inhibitors, (10) soluble guanylate cyclase stimulators, and (11) vasodilators (Figure 10.1). Depending on the severity of HF and individual patient factors, one or more of these classes of drugs are administered. Pharmacologic intervention for HF

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intends to provide the following benefits: reduced myocardial workload, decreased extracellular fluid volume, improved cardiac contractility, and a reduced rate of cardiac remodeling.

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ACE INHIBITORS

Captopril GENERIC ONLY
Enalapril VASOTEC
Fosinopril GENERIC ONLY
Lisinopril PRINIVIL, ZESTRIL
Quinapril ACCUPRIL
Ramipril ALTACE

ANGIOTENSIN RECEPTOR BLOCKERS

Candesartan ATACAND
Losartan COZAAR
Telmisartan MICARDIS
Valsartan DIOVAN

ARNI

Sacubitril/valsartan ENTRESTO

β–ADRENORECEPTOR BLOCKERS

Bisoprolol GENERIC ONLY
Carvedilol COREG, COREG CR
Metoprolol succinate TOPROL XL
Metoprolol tartrate LOPRESSOR

DIURETICS

Bumetanide BUMEX
Furosemide LASIX
Metolazone ZAROXOLYN
Torsemide DEMADEX

HCN CHANNEL BLOCKER

Ivabradine CORLANOR

INOTROPIC AGENTS

Digoxin LANOXIN
Dobutamine DOBUTREX
Dopamine GENERIC ONLY
Milrinone GENERIC ONLY

MINERALOCORTICOID RECEPTOR ANTAGONISTS

Eplerenone INSPRA
Spironolactone ALDACTONE

SGC STIMULATOR

Vericiguat VERQUVO

SGLT2 INHIBITORS

Dapagliflozin FARXIGA
Empagliflozin JARDIANCE

VASODILATORS

Hydralazine GENERIC ONLY
Isosorbide dinitrate DILATRATE-SR, ISORDIL
FDC Hydralazine/Isosorbide dinitrate BIDIL
Nitroglycerin GENERIC ONLY
Nitroprusside NIPRIDE, NITROPRESS

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Figure 10.1 Summary of drugs used to treat HF.ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; FDC = fixed-dose combination; HCN = hyperpolarization-activated cyclic nucleotide-gated; sGC = soluble guanylate cyclase; SGLT2 = sodium–glucose cotransporter 2.

II. PATHOPHYSIOLOGY OF HEART FAILURE

Knowledge of the physiology of cardiac muscle contraction is essential for understanding the compensatory responses evoked by the failing heart, as well as the actions of drugs used to treat HF. The myocardium, like smooth and skeletal muscle, responds to stimulation by depolarization of the membrane, which is followed by shortening of the contractile proteins and finishes with relaxation and return to the resting state (repolarization). Cardiac myocytes are interconnected in groups that respond to stimuli as a unit, contracting together whenever a single cell is stimulated. The force of contraction of the cardiac muscle is directly related to the concentration of free (unbound) cytosolic calcium. Therefore, agents that increase intracellular calcium levels (or that increase the sensitivity of the contractile machinery to calcium) increase the force of contraction (inotropic effect). Sustained, inappropriate, neurohormonal stimulation of cardiac tissue leads to impaired calcium homeostasis, heart failure, and arrhythmias. The movement of calcium in cardiac myocytes is illustrated in Figure 10.2.

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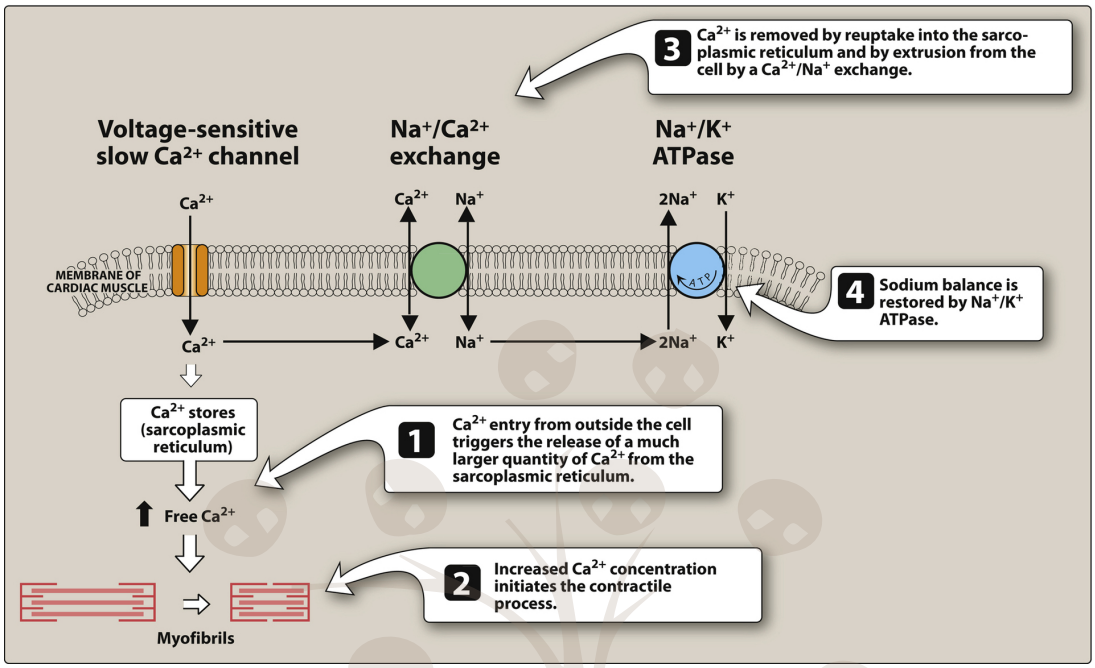

Figure 10.2 Ion movements during the contraction of cardiac muscle.ATPase = adenosine triphosphatase.

In HF, chronic activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS), oxidative stress and inflammation, and resistance to natriuretic peptides are associated with remodeling of cardiac tissue, loss of myocytes, hypertrophy, and fibrosis. These create a vicious cycle that, if left untreated, leads to death.

A. Compensatory physiologic responses in heart failure

The failing heart evokes four major compensatory mechanisms to enhance cardiac output, three of which have a negative impact on myocardial survival. Additional sequelae resulting from poor cardiac output are inflammation, oxidative stress, and resistance to natriuretic peptides (Figure 10.3).

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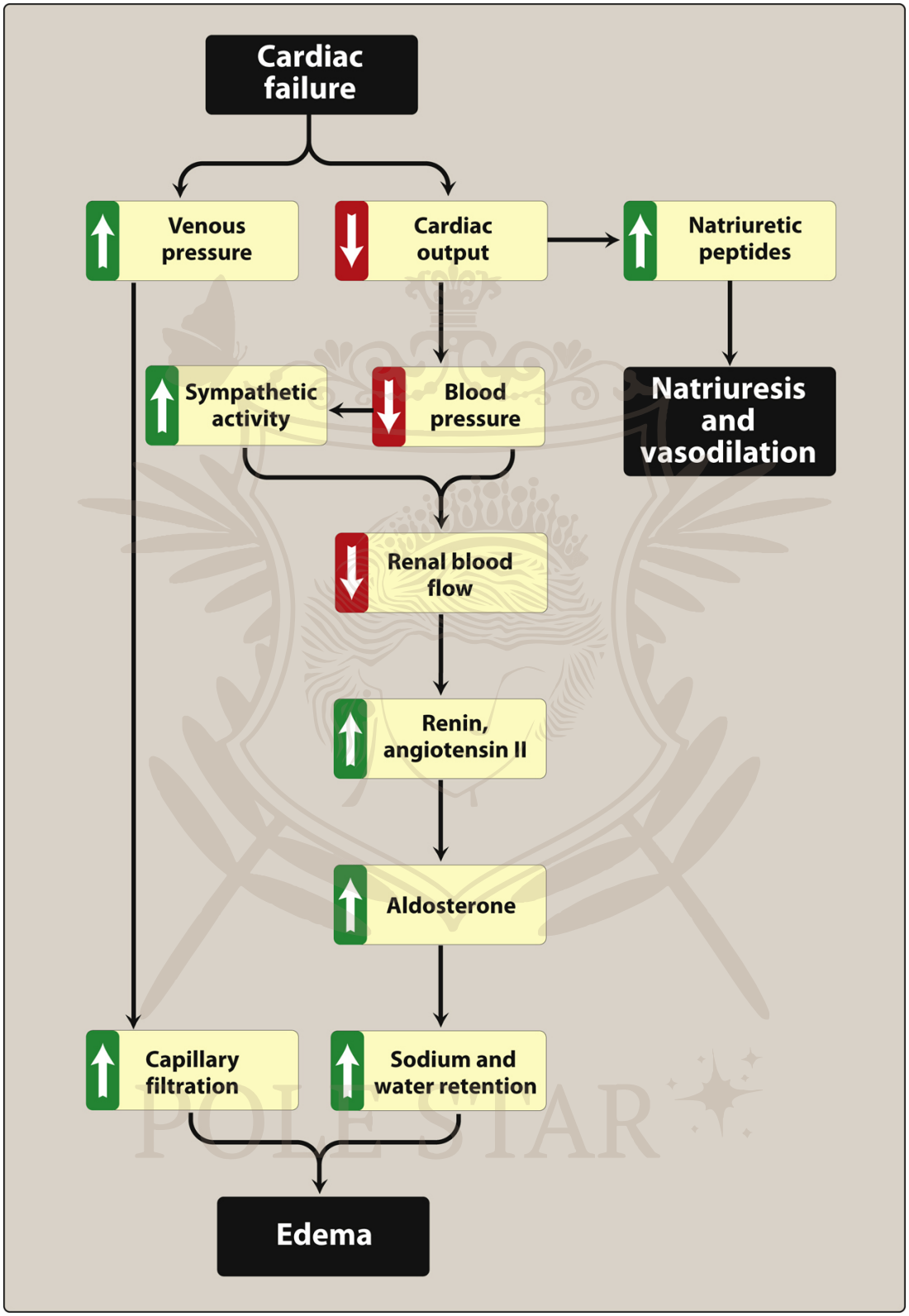

Figure 10.3 Cardiovascular consequences of HF.

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1.Increased sympathetic activity: Baroreceptors sense a decrease in blood pressure and activate the sympathetic nervous system. In an attempt to sustain tissue perfusion, this stimulation of β-adrenergic receptors results in an increased heart rate (chronotropy) and a greater force of contraction (inotropy) of the heart muscle. In addition, vasoconstriction enhances venous return and increases cardiac preload. An increase in preload (stretch on the heart) increases stroke volume, which, in turn, increases cardiac output. These compensatory responses increase the workload of the heart, which, in the long term, contributes to further decline in cardiac function.

2.Activation of the renin–angiotensin–aldosterone system: A fall in cardiac output decreases blood flow to the kidney, prompting the release of renin. Renin release is also stimulated by increased sympathetic activity, resulting in increased formation of angiotensin II and release of aldosterone. This leads to increased peripheral resistance (afterload) and retention of sodium and water (preload). As the blood volume increases, more blood is returned to the heart. If the heart is unable to pump this extra volume forward, venous pressure increases and peripheral and pulmonary edema occur. In addition, high levels of angiotensin II and aldosterone have direct detrimental effects on cardiac muscle, further enhancing cardiac remodeling, fibrosis, and inflammatory changes. Again, these compensatory responses increase the workload of the heart, contributing to continuous decline in cardiac function.

3.Activation of natriuretic peptides: An increase in preload also increases the release of natriuretic peptides. The natriuretic peptides, which include atrial (ANP), B-type (BNP), and C-type, have differing roles in HF; atrial and B-type natriuretic peptides have the largest impact on cardiac function. Activation of the natriuretic peptides ultimately results

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in vasodilation, natriuresis, inhibition of renin and aldosterone release, and a reduction in myocardial fibrosis. This beneficial response may improve cardiac function and HF symptoms.

4.Myocardial hypertrophy: Initially, stretching of the heart muscle leads to a stronger contraction of the heart. However, excessive elongation of the fibers eventually results in weaker contractions and a diminished ability to eject blood. This type of failure is termed “systolic failure” or HF with reduced ejection fraction (HFrEF) and is the result of the ventricle being unable to pump effectively. Alternatively, patients with HF may have “diastolic dysfunction,” a term applied when the ability of the ventricles to relax (lusitropy) and accept blood is impaired by structural changes such as hypertrophy. The thickening of the ventricular wall and subsequent decrease in ventricular volume reduces the ability of heart muscle to relax. In this case, the ventricle does not fill adequately, and the inadequacy of cardiac output is termed “diastolic HF” or HF with preserved ejection fraction (HFpEF). Diastolic dysfunction, in its pure form, is characterized by signs and symptoms of HF in the presence of a normal functioning left ventricle. However, both systolic and diastolic dysfunction commonly coexist in HF.

5.Increased inflammation and oxidative stress: A reduction in cardiac output in the setting of HFrEF leads to tissue hypoperfusion, neurohormonal activation, and volume overload. These, along with impaired cardiac energy metabolism, contribute to mitochondrial dysfunction, oxidative stress, and inflammation. In HFpEF, oxidative stress and inflammation caused by comorbidities (diabetes, obesity) are thought be triggers of cardiac dysfunction. The result in either HFrEF or HFpEF is impaired calcium regulation, cardiac hypertrophy, and cardiac myocyte death and fibrosis.

6.Resistance to natriuretic peptides: In HF syndromes, the heart releases natriuretic peptides (for example, ANP, BNP) in response to increases in afterload or

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preload. High levels of natriuretic peptides should generate vasodilation and natriuresis; however, these responses are often muted. The potential mechanisms for resistance to natriuretic peptides are prereceptor-, receptor-, or postreceptor mediated. Natriuretic peptide (NP) may be inactive or become inactivated by proteases (prereceptor), NP receptors may be become desensitized (receptor), or cyclic guanine monophosphate (cGMP), a second messenger of NP receptor activation, may be altered (postreceptor; Figure 10.4). Regardless of the mechanism of resistance to NP, the result is hypertrophy, fibrosis, inflammation, vasoconstriction, and reduced renal blood flow.

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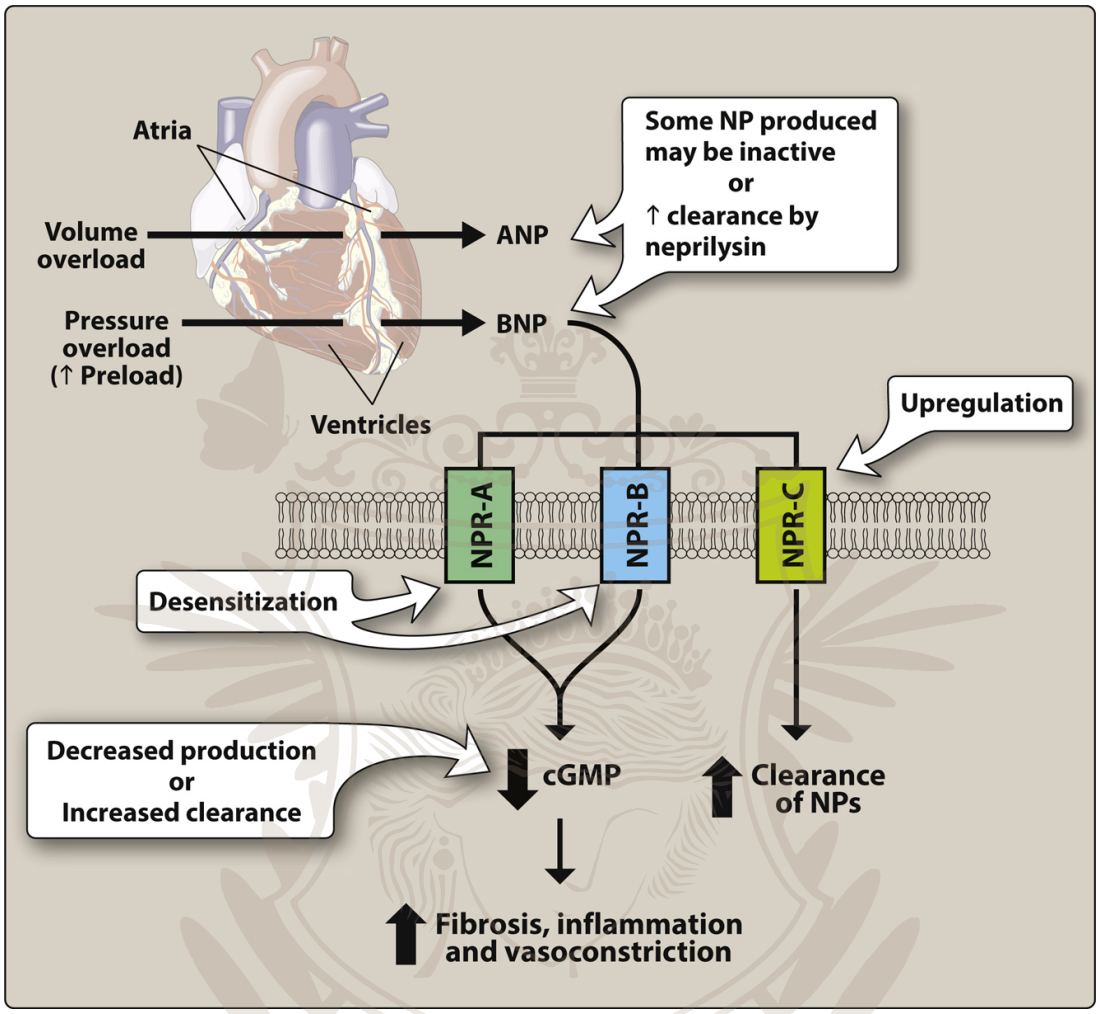

Figure 10.4 Resistance to natriuretic peptides.ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; cGMP = cyclic guanosine monophosphate; NP = natriuretic peptide; NPR = natriuretic peptide receptor.

B. Acute (decompensated) HF

If the compensatory mechanisms adequately restore cardiac output, HF is said to be compensated. If the compensatory mechanisms fail to maintain cardiac output, HF is considered decompensated, and the patient develops worsening HF signs and symptoms. Typical HF signs and symptoms include dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and peripheral edema.

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C. Therapeutic strategies in HF

Chronic HF is typically managed by fluid limitations (less than 1.5-2 L daily), low dietary intake of sodium (between 2 and 3 g/d), treatment of comorbid conditions, and judicious use of diuretics. In HFpEF, no medication has been shown to improve survival. However, inhibitors of the RAAS, inhibitors of the sympathetic nervous system, and diuretics can reduce symptoms. In HFrEF, multiple medication classes are typically combined to improve survival and/or reduce symptoms. Inotropic agents and intravenous vasodilators are reserved for acute signs and symptoms of HF and are used mostly in the inpatient setting. Drugs that may precipitate or exacerbate HF, such as nonsteroidal anti-inflammatory drugs, alcohol, nondihydropyridine calcium channel blockers, and some antiarrhythmic drugs, should be avoided if possible.

III. INHIBITORS OF THE RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM

The compensatory activation of the RAAS in HF leads to increased workload on the heart and a resultant decline in cardiac function. Therefore, inhibition of the RAAS is an important pharmacological target in the management of HF.

A. Angiotensin-converting enzyme inhibitors

ACE inhibitors are a part of standard pharmacotherapy in HFrEF. These drugs block the enzyme that cleaves angiotensin I to form the potent vasoconstrictor angiotensin II. They also diminish the inactivation of bradykinin (Figure 10.5).

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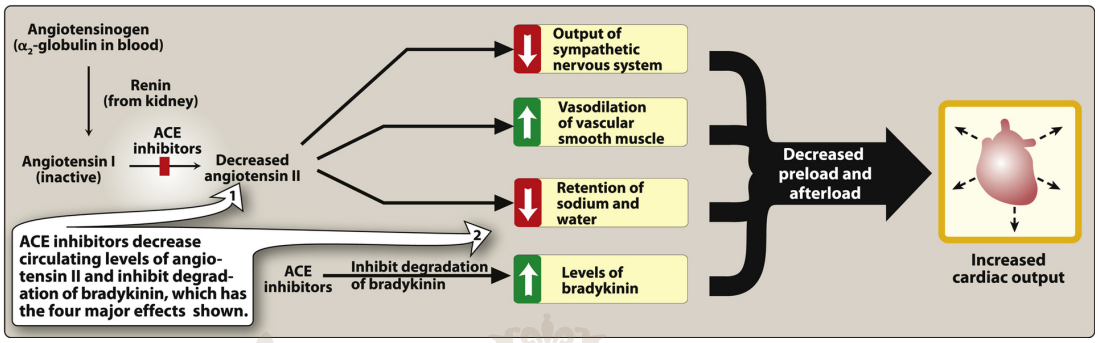

Figure 10.5 Effects of ACE inhibitors.[Note: The reduced retention of sodium and water results from two causes: decreased production of angiotensin II and aldosterone.]

1.Actions: ACE inhibitors decrease vascular resistance (afterload) and venous tone (preload), resulting in an overall increase in cardiac output. ACE inhibitors also blunt the usual angiotensin II–mediated increase in epinephrine and aldosterone seen in HF. ACE inhibitors improve clinical signs and symptoms of HF and have been shown to significantly improve patient survival in HFrEF.

2.Therapeutic use: ACE inhibitors may be considered for patients with asymptomatic and symptomatic HFrEF. Importantly, ACE inhibitors are indicated for patients with all stages of left ventricular failure. These agents should be started at low doses and titrated to target or maximally tolerated doses in the management of HFrEF. ACE inhibitors are also used in the treatment of hypertension in HFpEF (see Chapter 8 for more information on ACE inhibitors for hypertension). Patients who have had a recent myocardial infarction or are at high risk for a cardiovascular event also benefit from long-term ACE inhibitor therapy.

3.Pharmacokinetics: ACE inhibitors are adequately absorbed following oral administration. Food may decrease the absorption of *captopril* [KAP-toe-pril], so it should be taken on an empty stomach. Except for *captopril* and injectable

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enalaprilat [en-AL-a-pril-at], ACE inhibitors are prodrugs that require activation by hydrolysis via hepatic enzymes. Renal elimination of the active moiety is important for most ACE inhibitors except *fosinopril* [foe-SIN-oh-pril], which also undergoes excretion in the feces. Plasma half-life of the active compounds varies from 2 to 12 hours, although the inhibition of ACE may be much longer.

4.Adverse effects: These include postural hypotension, renal insufficiency, hyperkalemia, a persistent dry cough, and angioedema (rare). Because of the risk of hyperkalemia, potassium levels must be monitored, particularly with concurrent use of potassium supplements, potassium-sparing diuretics, or mineralocorticoid receptor antagonists. Serum creatinine levels should also be monitored, particularly in patients with underlying renal disease. The potential for symptomatic hypotension with ACE inhibitors is much more common if used concomitantly with a diuretic. ACE inhibitors are teratogenic and should not be used in pregnant women.

B. Angiotensin receptor blockers

Angiotensin receptor blockers (ARBs) are orally active compounds that are competitive antagonists of the angiotensin II type 1 receptor. Because ACE inhibitors inhibit only one enzyme responsible for the production of angiotensin II, ARBs have the advantage of more complete blockade of the actions of angiotensin II. In addition, ARBs do not affect bradykinin levels. Although ARBs have actions similar to those of ACE inhibitors, they are not therapeutically identical. Even so, ARBs are a substitute for patients who cannot tolerate ACE inhibitors.

1.Actions: Although ARBs have a different mechanism of action than ACE inhibitors, their actions on preload and afterload are similar. Their use in HF is mainly as a substitute in patients who cannot tolerate ACE inhibitors due to cough or angioedema, which are thought to be mediated by elevated

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bradykinin levels. ARBs are also used in the treatment of hypertension (see Chapter 8).

2. Pharmacokinetics: ARBs are orally active and are dosed once daily, with the exception of *valsartan* [val-SAR-tan], which is dosed twice daily. They are highly plasma protein bound. *Losartan* [loe-SAR-tan] differs in that it undergoes extensive first-pass hepatic metabolism, including conversion to an active metabolite. The other drugs have inactive metabolites. Elimination of metabolites and parent compounds occurs in urine and feces.

3. Adverse effects: ARBs have an adverse effect and drug interaction profile similar to that of ACE inhibitors. However, the ARBs have a lower incidence of cough and angioedema. Like ACE inhibitors, ARBs are contraindicated in pregnancy.

C. Mineralocorticoid receptor antagonists

Patients with HF have elevated levels of aldosterone due to angiotensin II stimulation and reduced hepatic clearance of the hormone. *Spironolactone* [spir-ON-oh-LAK-tone] and *eplerenone* [ep-LER-e-none] are antagonists of aldosterone at the mineralocorticoid receptor, thereby preventing sodium retention, myocardial hypertrophy, and hypokalemia. *Spironolactone* also has affinity for androgen and progesterone receptors and is associated with endocrine-related adverse effects such as gynecomastia and dysmenorrhea. *Eplerenone* is selective for the mineralocorticoid receptor. If endocrine-related adverse effects occur with *spironolactone*, transitioning to *eplerenone* is appropriate. Mineralocorticoid receptor antagonists (MRAs) are indicated in patients with symptomatic HFrEF or HFrEF and recent myocardial infarction or to prevent hospitalizations in HFpEF. Please see Chapter 9 for a full discussion of MRAs.

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IV. ANGIOTENSIN RECEPTOR–NEPRILYSIN INHIBITOR

Neprilysin is the enzyme responsible for degradation of vasoactive peptides, such as angiotensin I and II, bradykinin, and natriuretic peptides. Inhibition of neprilysin augments the activity of the vasoactive peptides. To help offset activation of RAAS and bradykinin while maintaining benefits of natriuretic peptides, an ARB is combined with a neprilysin inhibitor. This inhibits RAAS activation but does not further potentiate bradykinin. All of this minimizes the risk of angioedema (Figure 10.6).

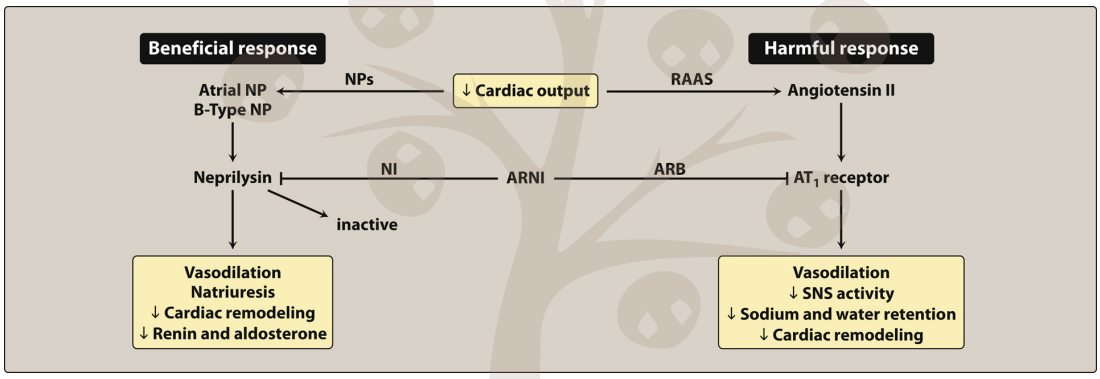

Figure 10.6 Effects of angiotensin receptor blocker–neprilysin inhibitors.ARB = angiotensin receptor blocker; ARNI = angiotensin - receptor–neprilysin inhibitor; AT1 = angiotensin type 1; NI, neprilysin inhibitor; NP = natriuretic peptide; RAAS = renin–angiotensin–aldosterone system; SNS = sympathetic nervous system.Modified from J. B.King , A. P.Bress , A. D.Reese , and M. A.Munger . Neprilysin inhibition in heart failure with reduced ejection fraction: a clinical review. *Pharmacotherapy*. 35: 823 (2015).

A. Sacubitril/Valsartan

Sacubitril [sak-UE-bi-tril]/*valsartan* is an ARNI.

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1.Actions: *Sacubitril*/*valsartan* combines the actions of an ARB with neprilysin inhibition. Inhibition of neprilysin results in increased concentration of vasoactive peptides, leading to natriuresis, vasodilation, and inhibition of fibrosis. Together, the combination decreases afterload, preload, and myocardial fibrosis. The ARNI combination improves survival and clinical signs and symptoms of HF, as compared with therapy with an ACE inhibitor.

2.Therapeutic use: *Sacubitril*/*valsartan* should replace an ACE inhibitor or ARB in patients with HFrEF who remain symptomatic on optimal doses of a β-blocker and an ACE inhibitor or ARB.

3.Pharmacokinetics: *Sacubitril*/*valsartan* is orally active, administered with or without food, and quickly breaks down into the separate components. *Sacubitril* is transformed to active drug by plasma esterases. Both drugs have a high volume of distribution and are highly bound to plasma proteins. *Sacubitril* is mainly excreted in the urine. The half-life of approximately 10 hours for both components allows for twice-daily dosing.

4.Adverse effects: The adverse-effect profile is similar to that of an ACE inhibitor or ARB. Because of the added reduction of afterload, hypotension is more common with an ARNI. Due to inhibition of neprilysin with *sacubitril*, bradykinin levels may increase and angioedema may occur. Therefore, the combination is contraindicated in patients with a history of hereditary angioedema or angioedema associated with an ACE inhibitor or ARB. To minimize risk of angioedema, an ACE inhibitor must be stopped at least 36 hours prior to starting *sacubitril/valsartan*.

Clinical Application 10.1: Use of Sacubitril/Valsartan in Heart Failure

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The ARNI *sacubitril/valsartan* is more effective than an ACE inhibitor or ARB in patients with mild to moderate symptomatic HFrEF. Hypotension is the most common adverse effect associated with an ARNI. To maximize the ability to tolerate an ARNI, most clinicians follow protocols that detail the transition from an ACE inhibitor. Optimally, patients should be on a target dose of an ACE inhibitor for at least 4 weeks, then stop the ACE inhibitor for at least 36 hours prior to transitioning to an ARNI. This washout period is required to minimize the risk of angioedema. Patients are most often transitioned to a moderate dose of ARNI to allow for tolerability and then reevaluated in 2 weeks with labs to assess serum creatinine and potassium. If the patient does not have symptomatic hypotension and labs are stable, *sacubitril/valsartan* should be increased to the target dose.

V. B-BLOCKERS

Although it may seem counterintuitive to administer drugs with negative inotropic activity in HF, evidence clearly demonstrates improved systolic function and reverse cardiac remodeling in patients receiving β-blockers. These benefits arise in spite of an occasional, initial exacerbation of symptoms. The benefit of β-blockers is attributed, in part, to their ability to prevent the changes that occur because of chronic stimulation from the sympathetic nervous system. These agents decrease heart rate and inhibit release of renin from the kidneys. In addition, β-blockers prevent the deleterious effects of norepinephrine on the cardiac muscle fibers, decreasing remodeling, hypertrophy, and cell death. Three β-blockers have shown benefit in HFrEF: *bisoprolol* [bis-oh-PROE-lol], *carvedilol* [KAR-ve-dil-ol], and long-acting *metoprolol succinate* [me-TOE-proe-lol SUK-si-nate]. *Carvedilol* is a nonselective β-adrenoreceptor antagonist that also blocks α-adrenoreceptors, whereas *bisoprolol* and *metoprolol succinate* are β_1-selective antagonists. [Note: The pharmacology of β-blockers is described in detail in Chapter 7.] β-Blockade is recommended for all patients with chronic, stable HFrEF and in those with HFpEF in need of heart rate control. *Bisoprolol*, *carvedilol*, and *metoprolol succinate* reduce morbidity and mortality associated with HFrEF. Treatment should be

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started at low doses and gradually titrated to target doses based on patient tolerance and vital signs. Both *carvedilol* and *metoprolol* are metabolized by the cytochrome P450 (CYP) 2D6 isoenzyme, and inhibitors of this metabolic pathway may increase levels of these drugs and increase the risk of adverse effects. In addition, *carvedilol* is a substrate of P-glycoprotein (P-gp). Increased effects of *carvedilol* may occur if it is coadministered with P-gp inhibitors. β-Blockers should also be used with caution with other drugs that slow atrioventricular (AV) conduction (negative dromotropy), such as *amiodarone*, *verapamil*, and *diltiazem*.

VI. DIURETICS

Diuretics reduce signs and symptoms of volume overload, such as dyspnea on exertion, orthopnea, and peripheral edema. Diuretics decrease plasma volume and, subsequently, decrease venous return to the heart (preload). This decreases cardiac workload and oxygen demand. Diuretics may also decrease afterload by reducing plasma volume, thereby further decreasing blood pressure. Loop diuretics are the most commonly used diuretics in HF. These agents are used for patients who require extensive diuresis and those with renal insufficiency. Since diuretics have not been shown to improve survival in HF, they should only be used to treat signs and symptoms of volume excess. Please see Chapter 9 for a full discussion of diuretics.

VII. HYPERPOLARIZATION-ACTIVATED CYCLIC NUCLEOTIDE–GATED CHANNEL BLOCKER

The hyperpolarization-activated cyclic nucleotide–gated (HCN) channel is responsible for the I_f current and setting the pace within the SA node. Inhibition of the HCN channel results in slowing of

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depolarization and a lower heart rate (Figure 10.7). Reduction in heart rate (negative chronotropy) is use and dose dependent.

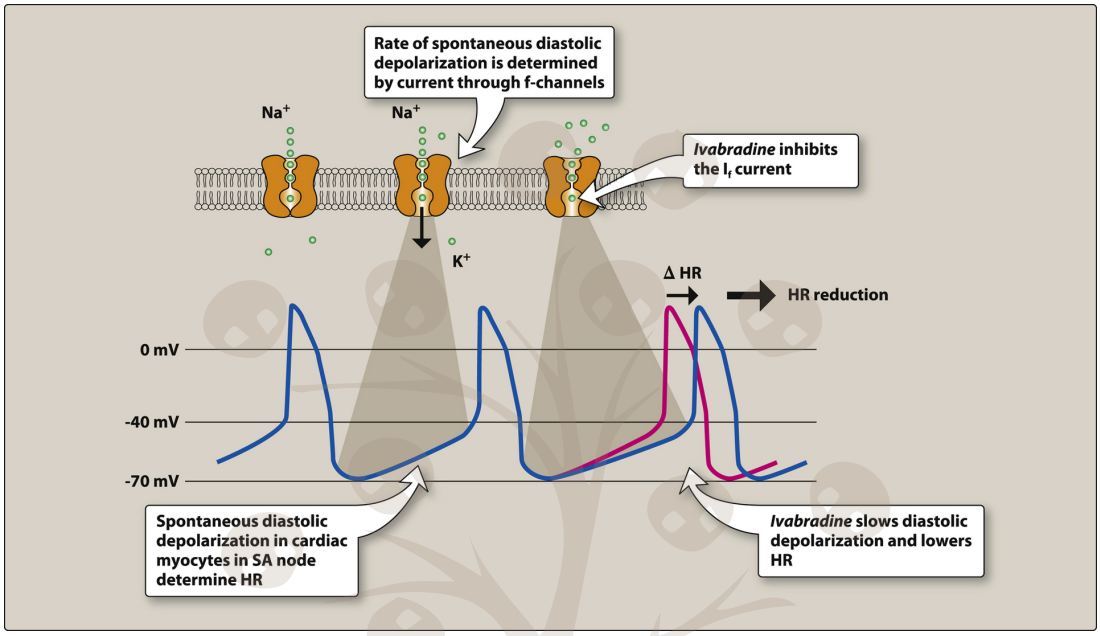

Figure 10.7 Effects of inhibition of I_f current with *ivabradine*.HR = heart rate; K^+ = potassium; Na^+ = sodium; SA = sinoatrial.Modified from P.Deedwania . Selective and specific inhibition of If with ivabradine for the treatment of coronary artery disease or heart failure. *Drugs*. 73: 1569 (2013).

A. Ivabradine

Ivabradine [eye-VAB-ra-deen] is the only drug in the class of HCN channel blockers.

1.Actions: By selectively slowing the I_f current in the SA node, reduction of heart rate occurs without a reduction in contractility, AV conduction, ventricular repolarization, or blood pressure. In patients with HFrEF, a slower heart rate increases stroke volume and improves symptoms of HF.

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2.Therapeutic use: *Ivabradine* is utilized in HFrEF to improve symptoms in patients who are in sinus rhythm with a heart rate above 70 beats per minute and are on optimized HF pharmacotherapy. Specifically, patients should be on an optimal dose of β-blocker or have a contraindication to β-blockers.

3.Pharmacokinetics: *Ivabradine* should be administered with meals to increase absorption. It undergoes extensive first-pass metabolism by CYP3A4 to an active metabolite, which is also a 3A4 substrate. *Ivabradine* has a high volume of distribution and is 70% protein bound. The half-life is 6 hours, which allows for twice-daily dosing.

4.Adverse effects: Bradycardia may occur with *ivabradine*, which may improve with dose reduction. Because *ivabradine* is mostly selective for the SA node, it is not effective for rate control in atrial fibrillation and has been shown to increase the risk of atrial fibrillation. *Ivabradine* inhibits similar channels in the eye, and luminous phenomena (for example, brightness or halos) may occur with therapy. This enhanced brightness may be ameliorated by dose reduction. *Ivabradine* should not be used in pregnancy or breast-feeding, with more advanced heart block, or with potent 3A4 inhibitors.

VIII. VASODILATORS

Vasodilators are often categorized into arterial or venous. However, most drugs perform both actions to varying degrees.

A. Arterial vasodilators

Hydralazine [hye-DRAL-a-zeen] is an arterial vasodilator that may be used to reduce afterload and is most often used in combination with an oral nitrate in chronic HF.

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1.Actions: The exact mechanism of *hydralazine* is not fully understood, but it is thought to reduce calcium in arteriole smooth muscle leading to vasodilation, afterload reduction, and increased cardiac output. *Hydralazine* also possesses antioxidant properties. Inhibiting oxidases prevents the breakdown of endogenous and exogenous nitric oxide (NO). Enhancing nitric oxide results in vasodilation and reduction in afterload and preload (Figure 10.8).

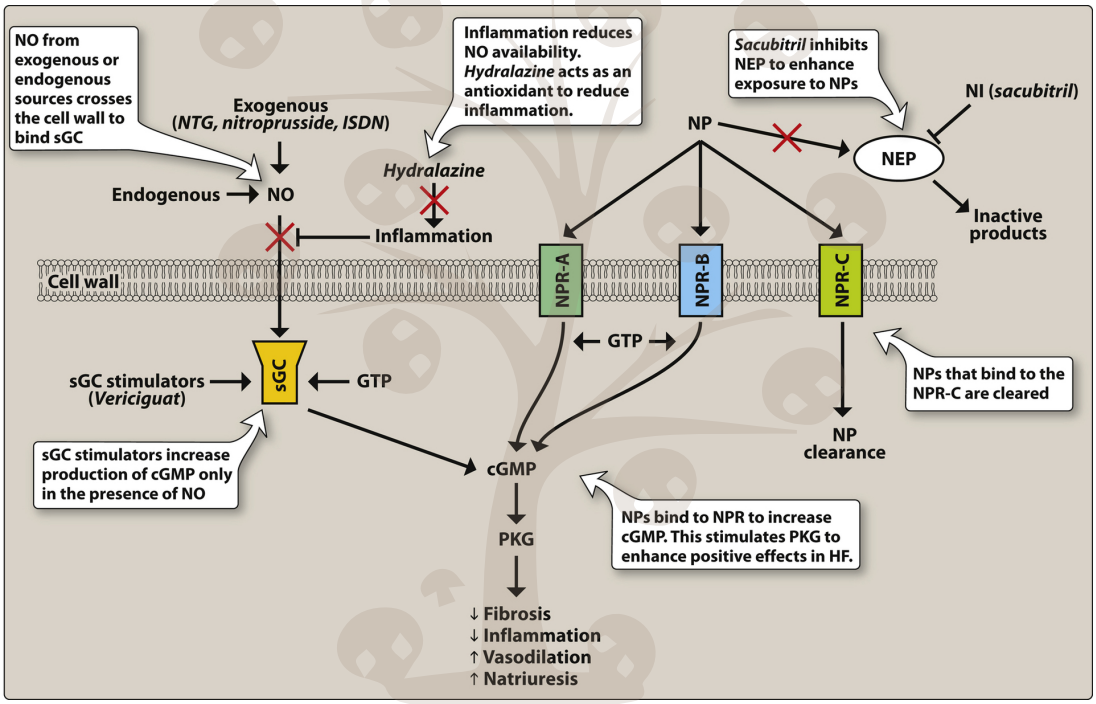

Figure 10.8 Physiologic action of nitric oxide and natriuretic peptides.ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; cGMP = cyclic guanosine monophosphate; CNP = C-type natriuretic peptide; GTP = guanosine triphosphate; ISDN = isosorbide dinitrate; NEP = neprilysin; NI = neprilysin inhibitor; NO = nitric oxide; NP = natriuretic peptide; NPR = natriuretic peptide receptor; NTG = nitroglycerin; PKG = protein kinase G; sGC = soluble guanylate cyclase.

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2. Therapeutic use: If a patient is intolerant of ACE inhibitors or ARBs, or if additional vasodilator response is required, a combination of *hydralazine* and *isosorbide dinitrate* [eye-soe-SOR-bide dye-NYE-trate] may be used. A fixed-dose combination of these agents has been shown to improve symptoms and survival in African-American patients with HFrEF on guideline-directed medical therapy (β-blocker plus ACE inhibitor or ARB). [Note: *Hydralazine* is also used for management of hypertension not controlled with first- or second-line therapies (see chapter 8).]

3. Pharmacokinetics: *Hydralazine* is available as an oral tablet and as a solution for intravenous or intramuscular injection. The oral formulation is used in HF and has 90% bioavailability. Food may reduce absorption; thus, most patients should take the drug without food. It is metabolized in the liver by acetylation to inactive metabolites. The half-life of *hydralazine* is short, as is the vasodilatory effect (2-4 hours). Thus, *hydralazine* is often dosed two to four times a day.

4. Adverse effects: Headache, dizziness, hypotension, reflex tachycardia, and edema are common adverse effects. To mitigate the latter adverse effects, *hydralazine* should only be used if the patient is already on a β-blocker and a diuretic. Rarely, *hydralazine* has been associated with drug-induced lupus.

B. Arterial and venous dilators

Nitrates (*nitroglycerin* [nye-troe-GLI-ser-in] and *isosorbide dinitrate* [eye-soe-SOR-bide dye-NYE-trate]) and *nitroprusside* [nye-troe-PRUS-ide] are vasodilators. Nitrates contribute more to venodilation than arterial dilation, whereas *nitroprusside* is more balanced between the two.

1. Actions: Nitrates and *nitroprusside* quickly convert to NO and bind soluble guanylate cyclase (sGC). This activation increases intracellular cyclic guanosine monophosphate

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(cGMP) in smooth muscle cells. Cyclic GMP activates protein kinase G, which ultimately results in release of intracellular calcium, thereby producing vasodilation. Dilation of venous blood vessels leads to a decrease in preload by increasing venous capacitance, and dilation of arteries reduces systemic vascular resistance, reduces afterload, and increases cardiac output.

2.Therapeutic use: *Isosorbide dinitrate* is most often utilized in combination with *hydralazine* for self-identified African-Americans with HFrEF. Black patients most often have lower NO bioavailability and less RAAS activation, which makes this combination especially useful as compared with other ethnicities. *Nitroglycerin* and *nitroprusside* are utilized in IV form for the treatment of acute decompensated HFrEF in patients with signs of congestion and elevated systemic vascular resistance.

3.Pharmacokinetics: *Isosorbide dinitrate* is rapidly absorbed and undergoes high first-pass metabolism to active metabolites. Onset is quick at approximately 30 minutes and duration of effect is 4 to 6 hours. As such, combining this formulation with *hydralazine* results in a close pharmacokinetic match.

Intravenous *nitroglycerin* has high first-pass hepatic metabolism and also is metabolized in the periphery by transferases and esterases. The onset is almost immediate upon administration and the half-life is 2 to 6 minutes. *Nitroprusside* biotransformation is unique in that it dissociates upon contact with sulfhydryl groups found on all cell walls to iron NO and cyanide groups. It also dissociates when in contact with hemoglobin to form cyanmethemoglobin and cyanide. Cyanide reacts with thiosulfate to form thiocyanate to allow for renal excretion. Due to a limited supply of thiosulfate and renal excretion of thiocyanate, high doses, longer infusions, and

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kidney disease predispose patients to cyanide toxicity with use of *nitroprusside*.

4.Adverse effects: Oral nitrates are usually well tolerated if started at low doses and increased slowly. However, headache and dizziness can be dose limiting. The most common adverse effect of both intravenous *nitroglycerin* and *nitroprusside* is hypotension and its related signs and symptoms. Both may rarely cause methemoglobinemia, and *nitroprusside* can cause cyanide toxicity.

IX. SODIUM–GLUCOSE COTRANSPORTER 2 INHIBITORS

A reduction in new diagnoses for HF was identified in clinical trials examining sodium–glucose cotransporter 2 (SGLT2) inhibitors in the treatment of type 2 diabetes. The pharmacology of SGLT2 inhibitors led to further study in HF. Abnormal increases in blood volume and interstitial fluid are common in HF and can contribute to elevated preload and afterload, which will exacerbate HF symptoms. SGLT2 inhibitors reduce plasma volume through glucosuria and natriuresis, thereby lowering preload and afterload. Although the mechanism is not fully understood, SGLT2 inhibitors may also increase cardiac efficiency by shifting energy metabolism toward oxidation of ketone bodies, reducing oxidative stress by inhibition of the myocardial sodium–hydrogen exchanger and preventing cardiac fibrosis through inhibition of myofibroblast differentiation.

A. Dapagliflozin and empagliflozin

SGLT2 inhibitors, such as *dapagliflozin* [dap-a-gli-FLOE-zin] and *empagliflozin* [em-pa-gli-FLOE-zin], reduce the development of HF in patients with a history of diabetes and reduce the risk of HF hospitalization and cardiovascular death in those with HFrEF.

@pharmacy_drug2

1.Actions: SGLT2 inhibitors mainly inhibit SGLT2 in the proximal tubule to reduce reabsorption of glucose and sodium. As such, they increase urinary glucose and sodium excretion, resulting in glucosuria, lower blood glucose, and natriuresis. Compared with diuretics, SGLT2 inhibitors may selectively reduce interstitial volume versus intravascular volume, thus limiting reflexive neurohormonal stimulation. Although there are multiple possible mechanisms responsible for the cardioprotective effects of SGLT2 inhibitors, the most plausible theory is inhibition of the sodium–hydrogen exchanger (NHE) prevents calcium overload and further contributes to natriuresis.

2.Therapeutic use: SGLT2 inhibitors should be considered in patients with symptomatic HFrEF who are on optimal HF pharmacotherapy with β-blockers, ACE inhibitors, and MRAs. Due to the natriuretic effects of SGLT2 inhibitors, dosages of diuretics may need to be titrated down following initiation of SGLT2 therapy. SGLT2 inhibitors are also indicated for patients with type 2 diabetes due to their enhanced excretion of glucose (see Chapter 24).

3.Pharmacokinetics: *Dapagliflozin* and *empagliflozin* are well absorbed and may be administered with and without food. Both are mainly metabolized via glucuronidation and exhibit minimal pharmacokinetic interactions. Parent drug and inactive metabolites are renally excreted. A similar half-life of approximately 12 hours for each allows for once-daily dosing.

Pharmacy Drug

Clinical Application 10.2: Use of SGLT2 Inhibitors in Patients With Heart Failure and Diabetes

SGLT2 inhibitors increase glucose excretion and induce natriuresis. Many patients with HF have concomitant type 2 diabetes mellitus and are taking diuretics, sulfonylureas, and/or insulin. These combinations may make the addition of an SGLT2 inhibitor difficult, considering that hypovolemia and hypoglycemia are more common in this scenario. If a patient is euvolemic and

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diabetes is under excellent control, reducing or stopping a diuretic, sulfonylurea, or insulin before initiation of the SGLT2 inhibitor is appropriate. If the patient is hypervolemic or has poor glucose control, no adjustment of other medications is required.

4.Adverse effects: Potential adverse effects include those related to volume depletion, renal insufficiency, and urogenital infections. SGLT2 inhibitors are more likely to cause hypoglycemia when combined with a sulfonylurea or insulin. Rare adverse effects, such as diabetic ketoacidosis, Fournier gangrene, and bone fractures, may occur. Although no data are available regarding safety, alternatives should be considered in pregnancy and breast-feeding.

X. SOLUBLE GUANYLATE CYCLASE STIMULATORS

Nitric oxide (NO) activates the enzyme-soluble guanylate cyclase (sGC) to stimulate production of cGMP. Oxidative stress and inflammation in HF inactivate endogenous NO and minimize the activation of sGC. This reduces the production of cGMP and contributes to vasoconstriction, fibrosis, and inflammation. sGC modulators increase sGC responsiveness to endogenous NO, thus correcting for the NO deficit in HF. This more physiologic approach to cGMP production, as compared with directly introducing exogenous NO, limits hypotension.

A. Vericiguat

Vericiguat [ver-i-SIG-ue-at] is a long-acting oral sGC stimulator.

1.Actions: *Vericiguat* directly stimulates sGC through a different binding site than NO and sensitizes sGC to endogenous NO. NO diffuses through cells to stimulate sGC to synthesize cGMP. An increase in cGMP activates protein kinase G to ultimately improve left ventricular compliance,

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vasodilate, reduce inflammation, and prevent hypertrophy and fibrosis (Figure 10.8). An sGC stimulator reduces the risk of HF hospitalization in those with evidence of recent acute decompensation.

2. **Therapeutic use:** An sGC stimulator may be started in patients with HFrEF who were recently hospitalized for HF and are on guideline-directed medical therapy.

3. **Pharmacokinetics:** *Vericiguat* is orally active and should be administered with food to increase bioavailability *Vericiguat* is primarily excreted in the urine as inactive metabolite and is also excreted to a lesser extent as unchanged drug in feces. Once-daily dosing is recommended due to a half-life of approximately 30 hours.

4. **Adverse effects:** The adverse effects are minimal with *vericiguat* and are due to its vasodilatory enhancement of NO. Hypotension, syncope, and anemia may occur. *Vericiguat* is contraindicated in pregnancy due to an increased risk of cardiac malformations and should not be used in breast-feeding. Use of *vericiguat* should be avoided with nitrates or phosphodiesterase inhibitors due to the risk of excessive hypotension.

XI. INOTROPIC DRUGS

Positive inotropic agents enhance cardiac contractility and, thus, increase cardiac output. Although these drugs act by different mechanisms, the inotropic action is the result of an increased cytoplasmic calcium concentration that enhances the contractility of cardiac muscle. The effects of ventricular function in heart failure, coupled with positive inotropes are reviewed in Figure 10.9. All positive inotropes in HFrEF that increase intracellular calcium concentration have been associated with reduced survival, especially in patients with HFrEF. For this reason, these agents, with

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the exception of *digoxin*, are only used for a short period mainly in the inpatient setting.

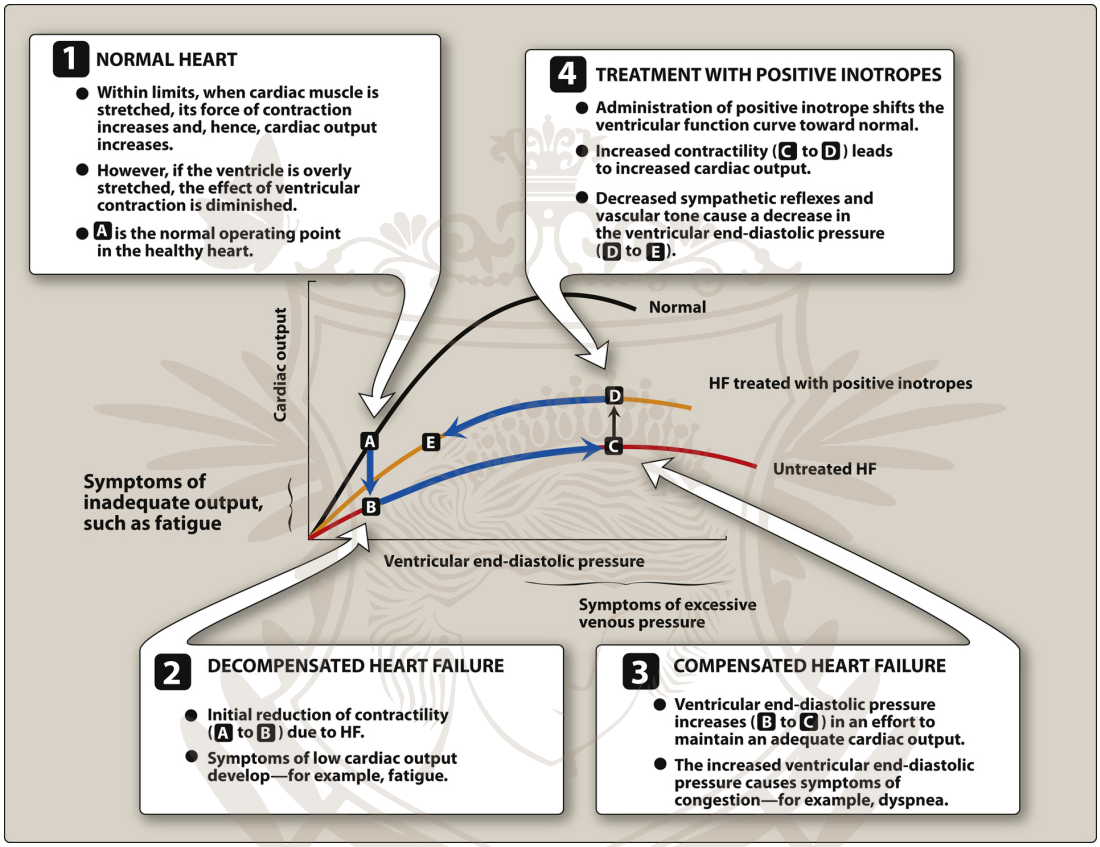

Figure 10.9 Ventricular function curves in the normal heart, in heart failure (HF), and in HF treated with positive inotropes.

A. Digitalis glycosides

The cardiac glycosides are often called digitalis or digitalis glycosides, because most of the drugs come from the digitalis (foxglove) plant. They are a group of chemically similar compounds that can increase the contractility of the heart muscle and, therefore, are used in treating HF. The digitalis glycosides have a low therapeutic index, with only a small difference between a therapeutic dose and doses that are toxic or even fatal. The only available agent is *digoxin* [di-JOX-in].

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1. Mechanism of action

a. Regulation of cytosolic calcium concentration: By inhibiting the Na^+/K^+-adenosine triphosphatase (ATPase) enzyme, *digoxin* reduces the ability of the myocyte to actively pump Na^+ from the cell. This ultimately results in a small but physiologically important increase in free Ca^{2+}, thereby leading to increased cardiac contractility.

b. Increased contractility of the cardiac muscle: *Digoxin* increases the force of cardiac contraction, causing cardiac output to more closely resemble that of the normal heart (Figure 10.9). Vagal tone is also enhanced, so both heart rate and myocardial oxygen demand decrease. *Digoxin* slows conduction velocity through the AV node, making it useful for atrial fibrillation.

c. Neurohormonal inhibition: Although the exact mechanism of this effect has not been elucidated, low-dose *digoxin* inhibits sympathetic activation with minimal effects on contractility. This effect is the reason a lower serum drug concentration is targeted in HFrEF.

2. Therapeutic use: *Digoxin* therapy is indicated in patients with HFrEF who are symptomatic on optimal HF pharmacotherapy. A low serum drug concentration of *digoxin* (0.5-0.9 ng/mL) is beneficial in HFrEF.

3. Pharmacokinetics: *Digoxin* is available in oral and injectable formulations. It has a large volume of distribution, because it accumulates in muscle. The dosage is based on lean body weight. In acute situations, such as symptomatic atrial fibrillation, a loading dose regimen is used. *Digoxin* has a long half-life of 30 to 40 hours. It is mainly eliminated intact by the kidney, requiring dose adjustment in renal dysfunction.

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4.Adverse effects: At low serum drug concentrations, *digoxin* is well tolerated. However, it has a very narrow therapeutic index. Anorexia, nausea, vomiting, blurred vision, or yellowish vision may be initial indicators of toxicity. When Na^+/K^+-ATPase is markedly inhibited by *digoxin*, the resting membrane potential may increase, which makes the membrane more excitable, increasing the risk of arrhythmias. Decreased levels of serum potassium (hypokalemia) predispose a patient to *digoxin* toxicity, because *digoxin* normally competes with potassium for the same binding site on the Na^+/K^+-ATPase pump. With the use of a lower serum drug concentration in HFrEF, toxic levels are infrequent. *Digoxin* is a substrate of P-gp, and inhibitors of P-gp, such as *clarithromycin*, *verapamil*, and *amiodarone*, can significantly increase *digoxin* levels, necessitating a reduced dose of *digoxin. Digoxin* should also be used with caution with other drugs that slow AV conduction, such as β-blockers, *verapamil*, and *diltiazem*.

B. β-Adrenergic agonists

β-Adrenergic agonists, such as *dobutamine* [doe-BUE-ta-meen] and *dopamine* [DOE-pa-meen], improve cardiac performance by causing positive inotropic effects and vasodilation (in the case of *dobutamine).* β-Adrenergic agonists ultimately lead to increased entry of calcium ions into myocardial cells and enhanced contraction (Figure 10.10). Both drugs must be given by intravenous infusion and are primarily used in the short-term treatment of acute decompensated HF in the hospital setting when cardiac output needs augmentation.

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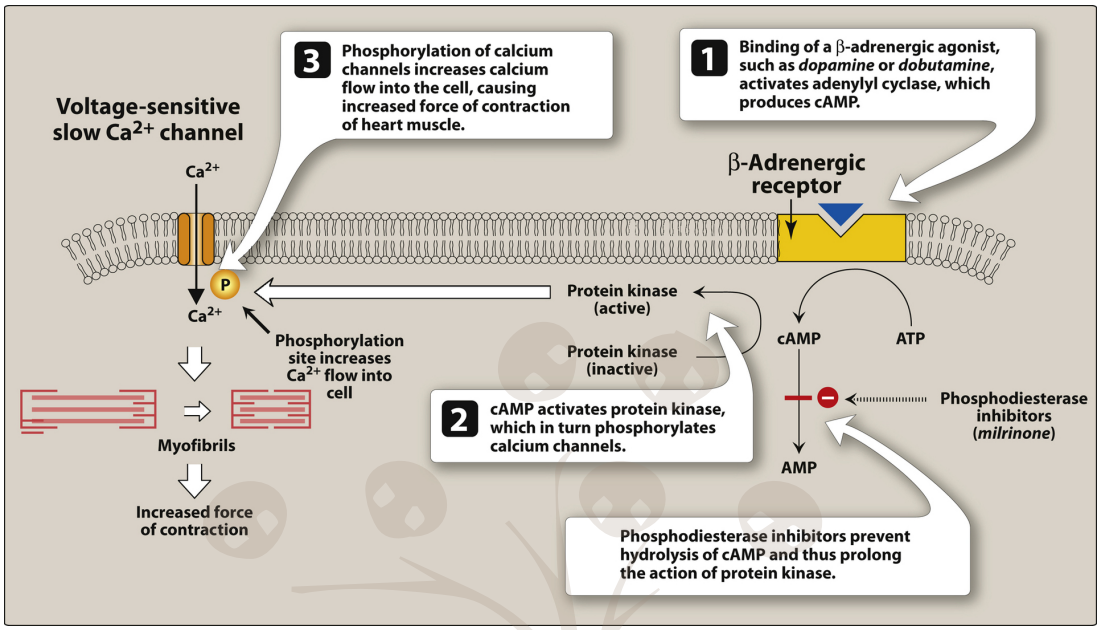

Figure 10.10 Sites of action by β-adrenergic agonists on heart muscle.AMP = adenosine monophosphate; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; P = phosphate.

C. Phosphodiesterase inhibitors

Milrinone [MIL-ri-none] is a phosphodiesterase inhibitor that increases the intracellular concentration of cAMP (Figure 10.10). Like β-adrenergic agonists, this results in an increase of intracellular calcium and, therefore, cardiac contractility. *Milrinone* is usually given by intravenous infusion for short-term treatment of acute decompensated HF with low cardiac output. However, *dobutamine* and *milrinone* may also be considered for intermediate-term treatment in the outpatient setting for palliative care. [Note: *Milrinone* can also reduce pulmonary vasculature resistance, making it useful for acute treatment of pulmonary hypertension and right heart failure.]

XII. ORDER OF THERAPY

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Guidelines have classified chronic HF into four stages, from least to most severe. Figure 10.11 shows a treatment strategy using this classification and the drugs described in this chapter. Note that as the disease progresses, polytherapy becomes the standard practice. In patients with decompensated HF, loop diuretics are often introduced first for relief of signs or symptoms of volume overload, such as dyspnea and peripheral edema. ACE inhibitors or ARBs (if ACE inhibitors are not tolerated) are added after the optimization of diuretic therapy. The dosage is gradually titrated to a maximally tolerated dosage and/or optimization of cardiac output. Historically, β-blockers were added after optimization of ACE inhibitor or ARB therapy; however, most patients newly diagnosed with HFrEF are initiated on both low doses of an ACE inhibitor and a β-blocker after initial stabilization. These agents are slowly titrated to optimal levels to increase tolerability. Mineralocorticoid receptor antagonists, fixed-dose *hydralazine* and *isosorbide dinitrate,* and SGLT2 inhibitors are initiated in patients who continue to have HF symptoms despite optimal doses of an ACE inhibitor and β-blocker. Once at an optimal ACE inhibitor or ARB dose, and if the patient remains symptomatic, either can be replaced by *sacubitril/valsartan.* Lastly, *digoxin*, *ivabradine*, and *vericiguat* are added for symptomatic benefit only in patients on optimal HF pharmacotherapy.

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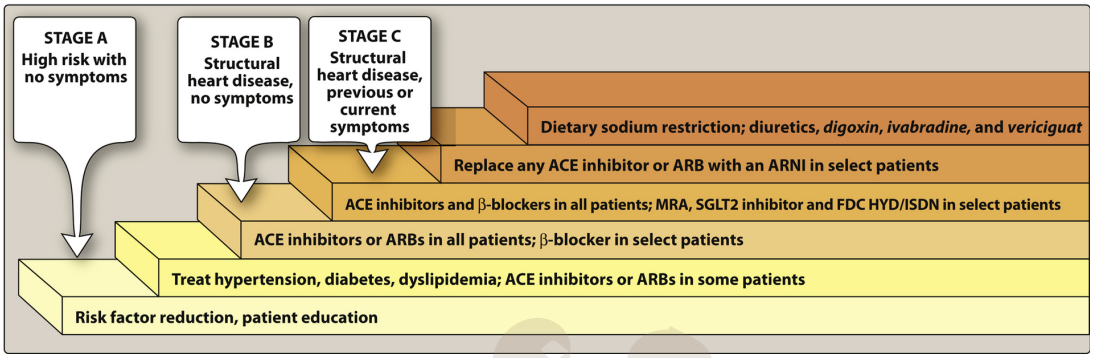

Figure 10.11 Treatment options for various stages of HF.ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; FDC = fixed-dose combination; HYD = hydralazine; ISDN = isosorbide dinitrate; MRA = mineralocorticoid receptor antagonist; SGLT2 = sodium–glucose cotransporter 2. Stage D (refractory symptoms requiring special interventions) is not shown.Modified from M.Jessup and S.Brozena . *N. Engl. J. Med*. 348: 2007. Copyright ©2003 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society and updated from C. W.Yancy , et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 136: 1 (2017).

Chapter summary

- After an initial insult, such as acute coronary syndrome, compensatory mechanisms that activate the sympathetic nervous system and RAAS help maintain adequate blood flow and pressure. If these mechanisms are not ameliorated, then further activation leads to inflammation, resistance to natriuretic peptides, worsening HF symptoms and death.
- The foundation of HF treatment is pharmacotherapy. These medications either block pathways that, when activated have negative consequences, or enhance pathways that have positive results. β-Blockers inhibit response to the sympathetic nervous system; ACE inhibitors, ARBs, and MRAs inhibit the RAAS; neprilysin inhibitors enhance the NP system; and sGC stimulators and vasodilators enhance NO.

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- Diuretics are used to minimize congestive symptoms in heart failure. They block the reabsorption of sodium and water, leading to diuresis and reduction in preload. Diuretics reduce plasma volume and may further activate RAAS. As such, if no signs or symptoms of volume overload are present, use of diuretics should be minimized.
- In some patients, heart rate is not adequately controlled on a maximized dose of a β-blocker. A few of these patients may not tolerate higher β-blocker doses due to hypotension or other adverse effects. *Ivabradine* can be added to a β-blocker to further control heart rate. *Ivabradine* blocks the HCN channel in the sinoatrial node to inhibit the I_f current. This slows diastolic depolarization and lowers heart rate.
- SGLT2 inhibitors inhibit the sodium–glucose cotransporter 2 in the proximal tubule to reduce the reabsorption of glucose and sodium. This reduces preload and afterload. Additional mechanisms may contribute to the benefit of SGLT2 inhibitors in HF, but more study is needed.
- Soluble guanylate cyclase stimulators enhance the ability of sGC to produce cGMP. Since NO is still required to activate sGC, *vericiguat* contributes to vasodilation by a more physiologic action, limiting excessive hypotension. Soluble GC stimulation also reduces hypertrophy, fibrosis, and vascular remodeling.
- Intravenous vasodilators (*nitroglycerin* and *nitroprusside*) provide NO to vascular smooth muscle to vasodilate. Rapid onset and short duration of action allows for titration to optimize preload, afterload, and cardiac output in acute decompensated HF.
- Positive inotropes (*milrinone*) are typically used intravenously in the hospital setting for acute decompensated HF. These drugs stimulate or prevent the breakdown of cAMP to eventually increase intracellular calcium. Calcium then binds to actin and myosin to increase contractility. Excess intracellular calcium increases the risk of arrhythmias and death if allowed to continue long term. Thus, positive inotropes are used for the shortest possible duration.
- *Digoxin* is still available for use, but has fallen out of favor due to the benefits realized with other HF drugs. At lower doses, *digoxin* is more likely to inhibit neurohormonal activation without positive inotropic effects. If used at all, lower trough serum digoxin concentrations of 0.5 to 0.9 ng/mL are targeted.

STUDY QUESTIONS

Choose the ONE best answer.

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10.1 A patient is newly diagnosed with HFrEF and is asymptomatic. Which is the most appropriate drug to initiate for symptomatic and survival benefits?

A. Dobutamine
B. Furosemide
C. Lisinopril
D. Sacubitril/valsartan

Correct answer = C. ACE inhibitors should be initiated in all patients, unless contraindicated, if they have HFrEF and are asymptomatic. This is known as stage B HF. Dobutamine and furosemide improve symptoms only. Sacubitril/valsartan will replace an ACE inhibitor if the patient remains symptomatic on optimal HF pharmacotherapy.

10.2 Which of the following statements best describes the action of ACE inhibitors on the failing heart?

A. Increased vascular resistance
B. Decreased cardiac output
C. Reduced preload
D. Increased aldosterone

Correct answer = C. ACE inhibitors decrease vascular resistance, decrease preload, decrease afterload, and increase cardiac output. In addition, ACE inhibitors blunt aldosterone release.

10.3 A Hispanic man with HFrEF currently takes maximally tolerated doses of metoprolol succinate and enalapril, along with moderate-dose furosemide. He is euvolemic but continues to have HF symptoms. The systolic blood pressure is low, but the patient does not have signs or symptoms of hypotension. Which is the best recommendation to improve HF symptoms and survival in this patient?

A. Stop enalapril, wait 36 hours, and start sacubitril/valsartan.

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B. Start digoxin.
C. Start fixed-dose hydralazine and isosorbide dinitrate.
D. Start spironolactone.

Correct answer = D. Because the patient is on optimal pharmacotherapy and continues to have symptoms, another agent is warranted. Adding low-dose spironolactone is unlikely to decrease the blood pressure and will confer a survival and symptomatic benefit. Changing to sacubitril/valsartan will likely worsen the low blood pressure. Digoxin will only improve symptoms and not improve survival. Fixed-dose hydralazine and isosorbide dinitrate would be appropriate if the patient were African American.

10.4 β-Blockers improve cardiac function in HF by:

A. Decreasing cardiac remodeling
B. Increasing heart rate
C. Increasing renin release
D. Activating norepinephrine

Correct answer = A. Although it seems counterintuitive to decrease heart rate in HF, β-blockers improve cardiac function by slowing heart rate, decreasing renin release, and preventing the direct effects of norepinephrine on cardiac muscle to decrease remodeling.

10.5 A 75-year-old white man has HFrEF and reports stable HF symptoms. His current drug therapy includes optimal-dose enalapril, carvedilol, and spironolactone. Which is the most appropriate recommendation to improve HF symptoms and survival?

A. Start fixed-dose hydralazine/isosorbide dinitrate.
B. Start ivabradine.
C. Replace enalapril with sacubitril/valsartan.
D. Start vericiguat.

Correct answer = C. Since the patient is on optimal doses of HF medications and he continues to have symptoms, replacing enalapril with sacubitril/valsartan

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is the only option that improves both symptoms and survival in a white patient.

10.6 A 55-year-old white man has HFrEF and reports stable HF symptoms. Current drug therapy includes optimal-dose sacubitril/valsartan, metoprolol succinate, and spironolactone. Which is the best recommendation to improve HF symptoms and survival?

A. Start dapagliflozin.
B. Start torsemide.
C. Start vericiguat.
D. Start milrinone.

Correct answer = A. Since the patient is on optimal doses of HF medications and he continues to have symptoms, adding an SGLT2 inhibitor is the only option that improves both symptoms and survival.

10.7 A man with HFrEF is taking carvedilol, candesartan, and spironolactone and is experiencing left breast pain and tenderness. There is no breast enlargement. What is the best option to minimize this symptom while continuing optimal management of HF?

A. Reduce the dose of spironolactone
B. Discontinue spironolactone and start eplerenone
C. Discontinue spironolactone and start enalapril
D. Continue spironolactone at current dose

Correct answer = B. Spironolactone is nonselective and can antagonize androgen and progesterone. As such, gynecomastia may occur in males. If this occurs, transitioning to selective eplerenone is most appropriate.

10.8 SGLT2 inhibitors improve HF symptoms through what mechanism?

A. Reducing preload

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B. Increasing cardiac output
C. Reducing blood glucose
D. Increasing ketone bodies

Correct answer = A. SGLT2 inhibitors reduce preload through glucosuria and natriuresis. Although glucosuria contributes to reduced blood glucose, the reduction of blood glucose is not the cause of improvement in HF symptoms.

10.9 A 49-year-old man is currently hospitalized for acute heart failure with a low cardiac output. The team would like to start a positive inotrope while continuing metoprolol succinate. What is the most appropriate positive inotrope to initiate?

A. Digoxin
B. Dobutamine
C. Milrinone
D. Diltiazem

Correct answer = C. Digoxin is not used as a positive inotrope in the inpatient setting for acute decompensated HF. Dobutamine agonizes β-receptors to increase cAMP and increase contractility. If the patient remains on a β-blocker, there is competitive action at the receptor, which may limit dobutamine efficacy. Milrinone increases cAMP through inhibition of PDE-3 and thus does not interact with metoprolol. Diltiazem is a negative inotrope and should not be used in HFrEF.

10.10 An 85-year-old woman has HFpEF. She is not on any medications for HF and has elevated blood pressure. Which is the most appropriate drug to initiate?

A. Ramipril
B. Sacubitril/valsartan
C. Empagliflozin
D. FDC hydralazine/isosorbide dinitrate

Correct answer = A. No medication has been proven to improve survival in HFpEF. However, ACE inhibitors, ARBs, and MRAs are utilized to reduce

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afterload, decrease BP, and improve symptoms in HFpEF. Sacubitril/valsartan, SGLT2 inhibitors and FDC hydralazine/isosorbide dinitrate have only shown benefit in HFrEF.

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11

Antiarrhythmics

Shawn David Anderson, Lisa Deacon

I. OVERVIEW

In contrast to skeletal muscle, which contracts only when it receives a stimulus, the heart contains specialized “pacemaker cells” that generate rhythmic action potentials in the absence of external stimuli. This is referred to as “automaticity.” These cells differ from other myocardial cells because they exhibit a slow, spontaneous depolarization during diastole (phase 4), caused by an inward positive current carried by sodium and calcium ions. This depolarization is fastest in the sinoatrial (SA) node (the initiation site of the action potential), and it decreases throughout the normal conduction pathway through the atrioventricular (AV) node to the bundle of His and the Purkinje system. Dysfunction of impulse generation or conduction at any site in the heart can cause an abnormality in cardiac rhythm, an arrhythmia. This chapter reviews the drugs used to treat arrhythmias (Figure 11.1) and their various mechanisms of action. Antiarrhythmic drugs are typically classified based on their effect on the cardiac action potential. Figure 11.2 illustrates the cardiac action potential and highlights major ions contributing to depolarization and repolarization of cardiac myocytes. This will be explained in more detail throughout the chapter.

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CLASS I (Na⁺-channel blockers)

Disopyramide NORPACE
Flecainide TAMBOCOR
Lidocaine XYLOCAINE
Mexiletine GENERIC ONLY
Procainamide GENERIC ONLY
Propafenone RYTHMOL
Quinidine GENERIC ONLY

CLASS II (β-adrenoreceptor blockers)

Atenolol TENORMIN
Esmolol BREVIBLOC
Metoprolol LOPRESSOR, TOPROL-XL

CLASS III (K⁺ channel blockers)

Amiodarone CORDARONE, PACERONE
Dofetilide TIKOSYN
Dronedarone MULTAQ
Ibutilide CORVERT
Sotalol BETAPACE, SORINE

CLASS IV (Ca²⁺ channel blockers)

Diltiazem CARDIZEM, CARTIA, TIAZAC
Verapamil CALAN, VERELAN

OTHER ANTIARRHYTHMIC DRUGS

Adenosine ADENOCARD
Digoxin LANOXIN
Magnesium sulfate GENERIC ONLY
Ranolazine RANEXA

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A L G r a w a n y

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Figure 11.1 Summary of antiarrhythmic drugs.

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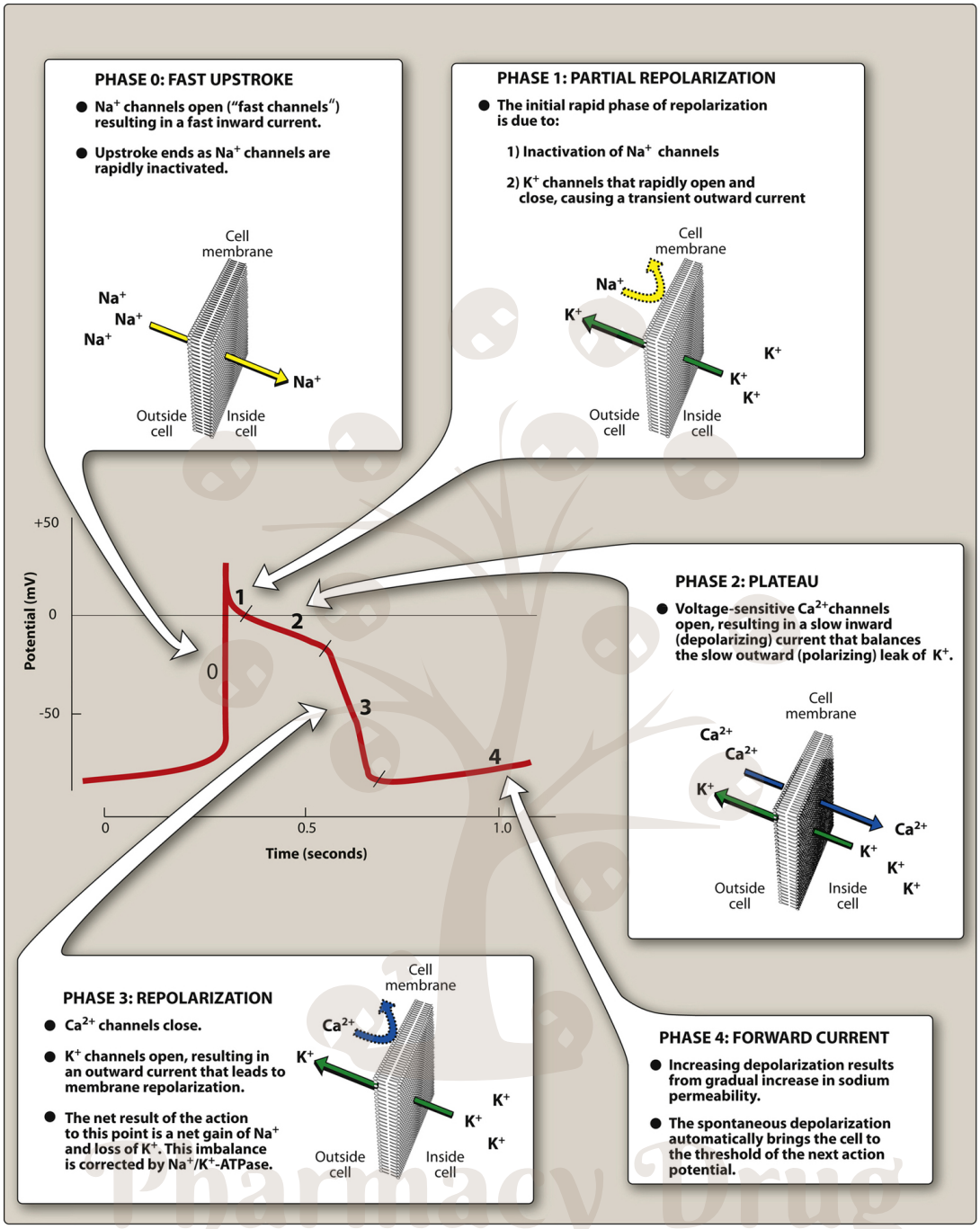

Figure 11.2 Action potential of a cardiac myocyte.ATPase = adenosine triphosphatase.

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II. INTRODUCTION TO THE ARRHYTHMIAS

Arrhythmias are caused by abnormalities in impulse formation and conduction in the myocardium. Arrhythmias present as a complex family of disorders with a variety of symptoms. To make sense of this large group of disorders, it is useful to organize arrhythmias into groups according to anatomic site of the abnormality: the atria, the AV node, or the ventricles. Figure 11.3 summarizes several common arrhythmias.

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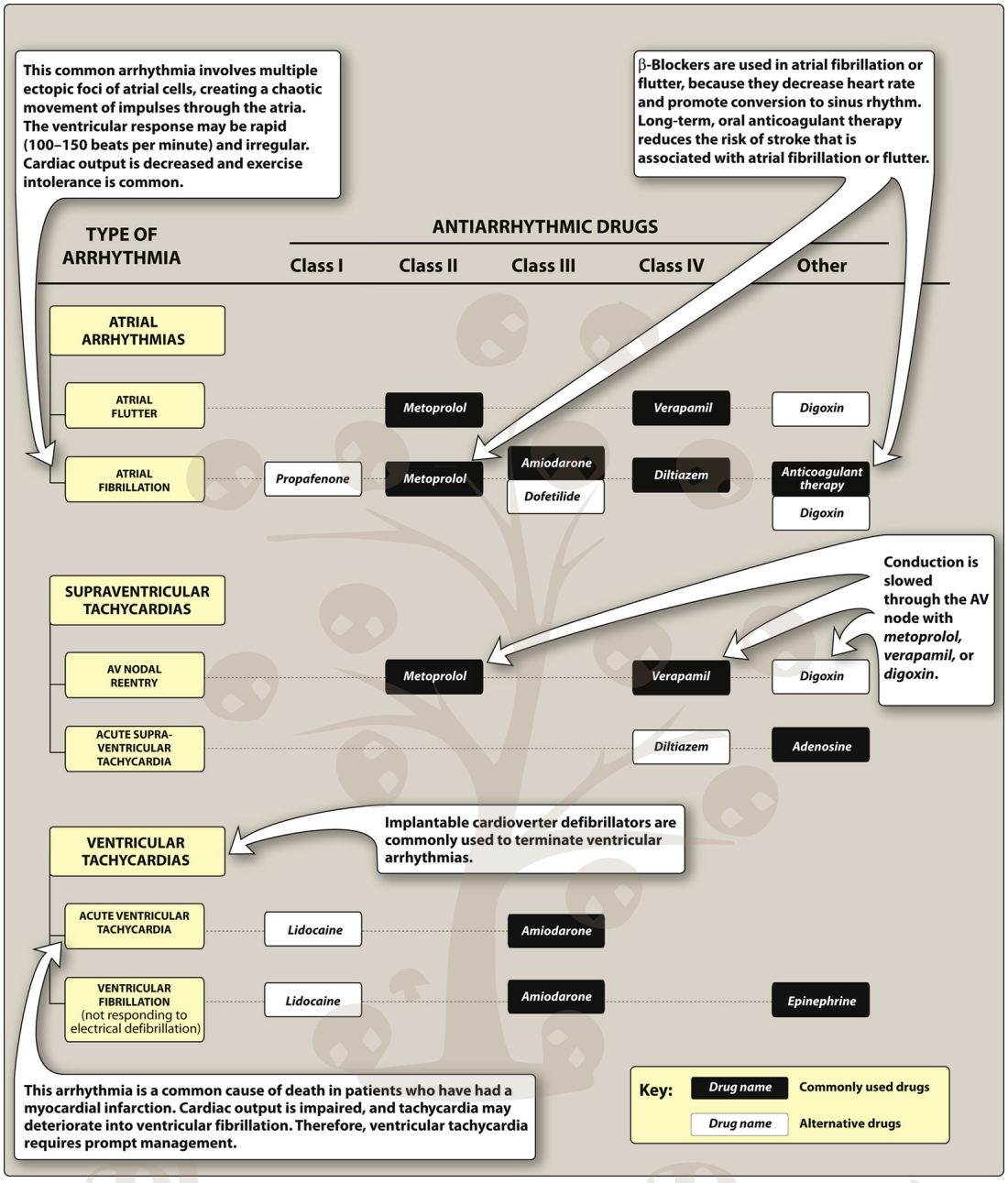

Figure 11.3 Therapeutic indications for some commonly encountered arrhythmias.AV = atrioventricular.

A. Causes of arrhythmias

Most arrhythmias arise either from aberrations in impulse generation (abnormal automaticity) or from a defect in impulse conduction.

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1.Abnormal automaticity: The SA node shows a faster rate of discharge than do other pacemaker cells, and thus, it normally sets the pace of contraction for the myocardium. If cardiac sites other than the SA node show enhanced automaticity, they may generate competing stimuli and arrhythmias may arise. Most of the antiarrhythmic agents suppress automaticity by blocking either sodium (Na^+) or calcium (Ca^{2+}) channels to reduce the ratio of these ions to potassium (K^+). This decreases the slope of phase 4 (diastolic) depolarization and/or raises the threshold of discharge to a less negative voltage, leading to an overall decrease in frequency of discharge. This effect is more pronounced in cells with ectopic pacemaker activity than in normal cells.

2.Abnormalities in impulse conduction: Impulses from higher pacemaker centers are normally conducted down pathways that bifurcate to activate the entire ventricular surface (Figure 11.4). A phenomenon called reentry can occur if a unidirectional block caused by myocardial injury or a prolonged refractory period results in an abnormal conduction pathway. Reentry is the most common cause of arrhythmias, and it can occur at any level of the cardiac conduction system. This short-circuit pathway results in re-excitation of cardiac muscle, causing premature contraction or a sustained arrhythmia. Antiarrhythmic agents prevent reentry by slowing conduction (class I drugs) and/or increasing the refractory period (class III drugs), thereby converting a unidirectional block into a bidirectional block.

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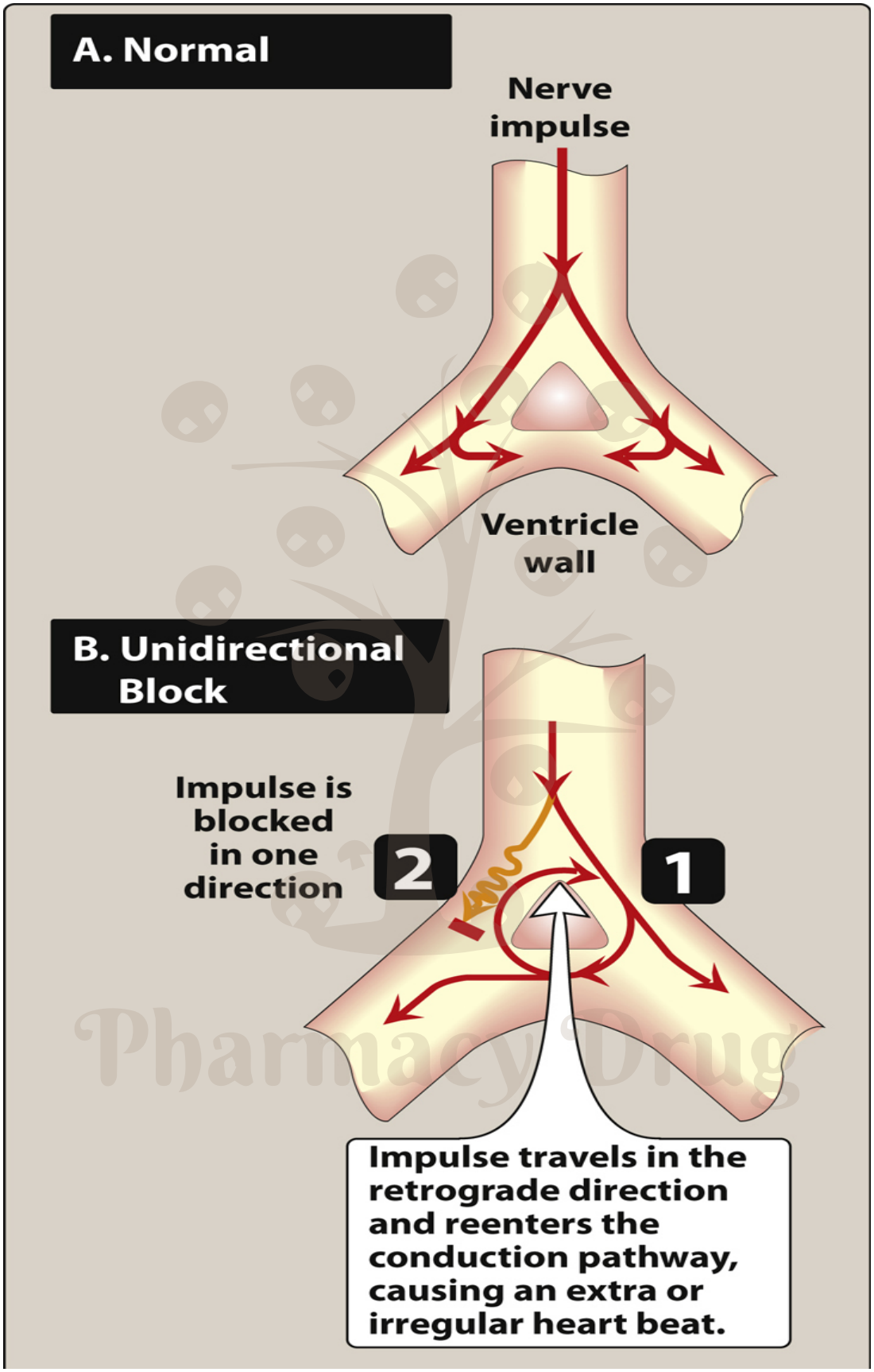

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Figure 11.4 Schematic representation of reentry.Modified from J. A.Beven and J. H.Thompson . *Essentials of Pharmacology*. Philadelphia, PA, Wolters Kluwer (1983).

B. Antiarrhythmic drugs

Antiarrhythmic drugs can modify impulse generation and conduction to prevent arrhythmias or to reduce symptoms associated with arrhythmias. Unfortunately, many of the antiarrhythmic agents are known to have dangerous proarrhythmic actions, that is, to cause arrhythmias. Inhibition of K^+ channels widens the action potential and can, thus, prolong the QT interval. If prolongation is excessive, these drugs increase the risk of developing life-threatening ventricular tachyarrhythmias (torsades de pointes). The most common cause of QT prolongation is drug-induced, although other conditions (for example, ischemia and hypokalemia) and genetic abnormalities may contribute. In addition to antiarrhythmics, many other drugs are known to prolong the QT interval, such as macrolide antibiotics and antipsychotics. Caution should be employed when combining drugs with additive effects on the QT interval or when giving QT-prolonging antiarrhythmic agents with drugs known to inhibit their metabolism.

Antiarrhythmic drugs can be classified (Vaughan–Williams classification) according to their predominant effects on the action potential (Figure 11.5). Although this classification is convenient, it has some limitations. Many antiarrhythmic drugs have actions relating to more than one class or may have active metabolites with a different class of action, or may have an action that does not meet any formal classification.

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CLASSIFICATION OF DRUG	MECHANISM OF ACTION	DRUG NAME	ADVERSE EFFECTS
IA	**Na^+ channel blocker** Slows Phase 0 depolarization in cardiac myocytes	*Disopyramide* *Procainamide* *Quinidine*	Ventricular arrhythmias, QT prolongation, acute heart failure, syncope, dizziness, rash, hemolytic anemia, anticholinergic effects ***Quinidine:*** Cinchonism, hemolytic anemia, visual disturbances, esophagitis ***Procainamide:*** Lupus-like syndrome, hypotension
IB	**Na^+ channel blocker** Shortens Phase 3 repolarization in cardiac myocytes	*Lidocaine* *Mexiletine*	Worsening ventricular arrhythmias, syncope, dizziness, tremor, ataxia, paresthesia, confusion, seizures, liver failure ***Mexiletine:*** Nausea/vomiting, dyspepsia, dysphagia
IC	**Na^+ channel blocker** Markedly slows Phase 0 depolarization in cardiac myocytes	*Flecainide* *Propafenone*	Bradycardia, QT prolongation, worsening ventricular arrhythmias, acute HF, syncope, dizziness, hypotension, constipation, headache, tremor, visual disturbances ***Propafenone:*** Bronchospasms, liver failure, agranulocytosis, anemia, edema
II	**β-Adrenoreceptor blocker** Inhibits Phase 4 depolarization in SA and AV nodes	*Atenolol* *Esmolol* *Metoprolol*	Bradycardia, heart block, hypotension, worsening heart failure, dizziness, bronchospasm ***Metoprolol:*** Exercise intolerance, fatigue, sleep disturbances, depression, sexual dysfunction, hyperglycemia, hypertriglyceridemia
III	**K^+ channel blocker** Prolongs Phase 3 repolarization in cardiac myocytes	*Amiodarone** *Dofetilide* *Dronedarone** *Ibutilide* *Sotalol#*	***Amiodarone:*** Bradycardia, QT prolongation, worsening ventricular arrhythmias, syncope, dizziness, hypotension, pulmonary toxicity (pneumonitis, fibrosis), hepatic failure, transaminitis, peripheral neuropathy, paresthesia, hypo- and hyperthyroidism, rash, blue-gray skin discoloration, corneal deposits, optic neuritis
IV	**Ca^{2+} channel blocker** Inhibits action potential in SA and AV nodes	*Diltiazem* *Verapamil*	Bradycardia, heart block, acute heart failure, peripheral edema, hypotension, dizziness, constipation, gynecomastia, sexual dysfunction ***Verapamil:*** Gingival hyperplasia, constipation
Other	**Various mechanisms**	*Adenosine* *Digoxin* *Magnesium sulfate* *Ranolazine*	***Adenosine:*** Transient arrhythmias, dizziness, chest pain, dyspnea, palpitations, hypotension, nervousness, headache ***Digoxin:*** Bradycardia, worsening ventricular arrhythmias, syncope, hypokalemia, hyperkalemia, anorexia, dizziness, rash, hallucinations, blurred vision and xanthopsia ***Magnesium:*** Hypotension, vasodilation, flushing ***Ranolazine:*** QT prolongation, worsening ventricular arrhythmias, syncope, dizziness, headache, hallucinations, blurred vision, vertigo, nausea, constipation

Figure 11.5 Actions and adverse effects of antiarrhythmic drugs.AV = atrioventricular; SA = sinoatrial; * = exhibits class I, II, III, and IV actions; # = also exhibits non-selective β-blocker activity.

III. CLASS I ANTIARRHYTHMIC DRUGS

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Class I antiarrhythmic drugs act by blocking voltage-sensitive Na^+ channels. They bind more rapidly to open or inactivated Na^+ channels than to channels that are fully repolarized. Therefore, these drugs show a greater degree of blockade in tissues that are frequently depolarizing. This property is called “use-dependence” (or “state-dependence”), and it enables these drugs to block cells that are discharging at an abnormally high frequency, without interfering with the normal beating of the heart.

The use of Na^+ channel blockers has declined due to their proarrhythmic effects, particularly in patients with reduced left ventricular function and atherosclerotic heart disease. Class I drugs are further subdivided into three groups according to their effect on the duration of the cardiac action potential (Figure 11.5).

A. Class IA antiarrhythmic drugs: quinidine, procainamide, and disopyramide

Quinidine [KWIH-nih-deen] is the prototype class IA drug. Other agents in this class include *procainamide* [proe-KANE-a-mide] and *disopyramide* [dye-soe-PEER-a-mide]. Because of their concomitant class III activity, they can precipitate arrhythmias that can progress to ventricular fibrillation.

1. Mechanism of action: *Quinidine* binds to open and inactivated Na^+ channels and prevents Na^+ influx, thus slowing the rapid upstroke during phase 0 (Figure 11.6). It decreases the slope of phase 4 spontaneous depolarization, inhibits K^+ channels, and blocks Ca^{2+} channels. Because of these actions, it slows conduction velocity and increases refractoriness. *Quinidine* also has mild α-adrenergic blocking and anticholinergic actions. Although *procainamide* and *disopyramide* have actions similar to those of *quinidine*, there is less anticholinergic activity with *procainamide* and more with *disopyramide.* Neither *procainamide* nor *disopyramide* has α-blocking activity. *Disopyramide* produces a greater negative inotropic effect, and unlike the other drugs, it causes peripheral vasoconstriction.

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Pharmacy Drug

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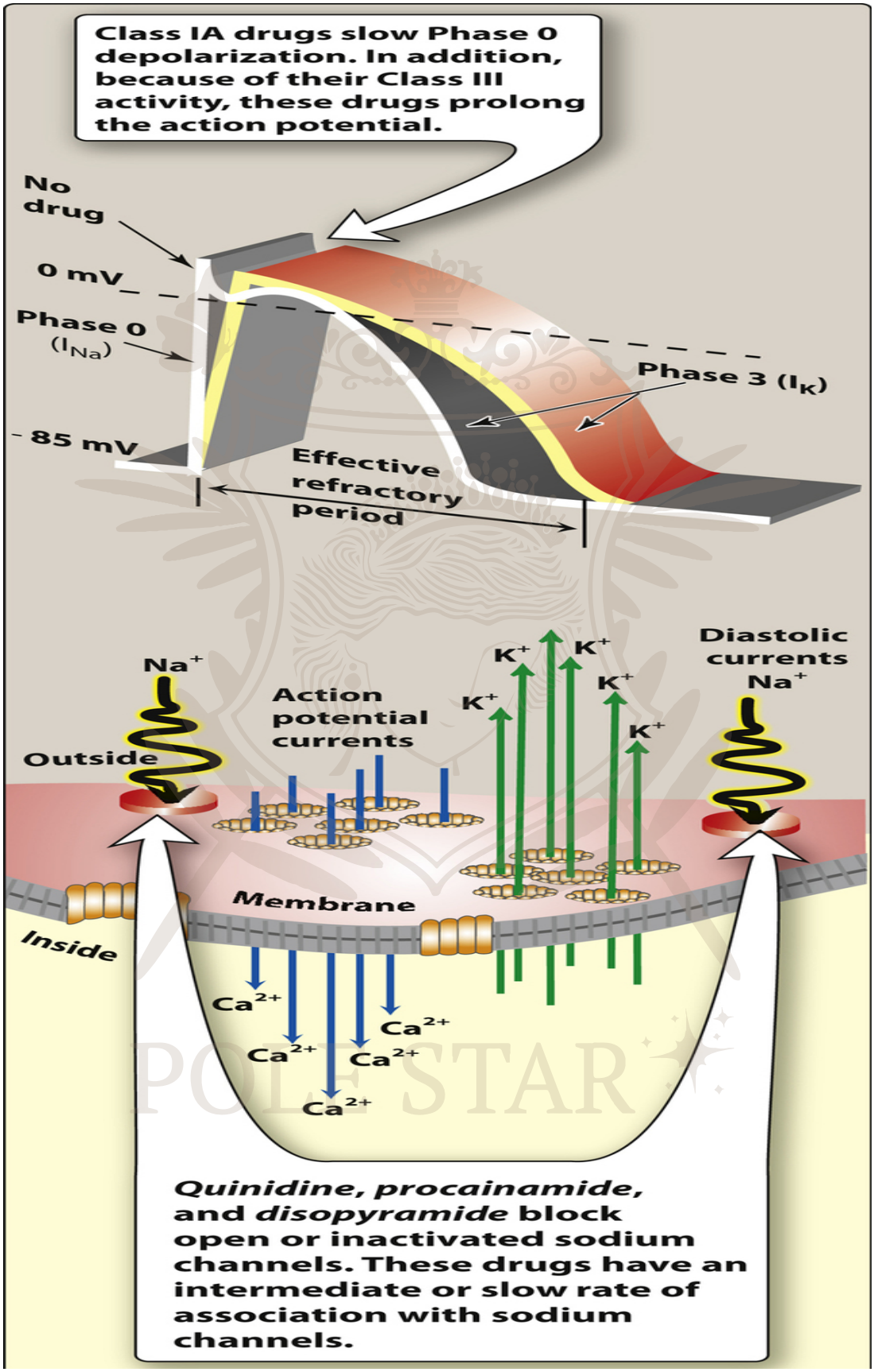
Class IA drugs slow Phase 0 depolarization. In addition, because of their Class III activity, these drugs prolong the action potential.
No drug
0 mV
Phase 0 (I_{Na})
Phase 3 (I_K)
- 85 mV
Effective refractory period
Diastolic currents
Na^+
Action potential currents
K^+
K^+
K^+
K^+
K^+
Outside
Membrane
Inside
Ca^{2+}
Ca^{2+}
Ca^{2+}
Ca^{2+}
Ca^{2+}
Quinidine, procainamide, and *disopyramide* block open or inactivated sodium channels. These drugs have an intermediate or slow rate of association with sodium channels.

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Figure 11.6 Schematic diagram of the effects of class IA agents. I_{Na} and I_K are transmembrane currents due to the movement of Na^+ and K^+, respectively.

2. Therapeutic uses: *Quinidine* is used in the treatment of a wide variety of arrhythmias, including atrial, AV junctional, and ventricular tachyarrhythmias. *Procainamide* is only available in an intravenous formulation and may be used to treat acute atrial and ventricular arrhythmias. However, electrical cardioversion or defibrillation and *amiodarone* have mostly replaced *procainamide* in clinical practice. *Disopyramide* can be used as an alternative treatment of ventricular arrhythmias and may also be used for rhythm control in atrial fibrillation or flutter.

3. Pharmacokinetics: *Quinidine sulfate* or *gluconate* is rapidly and well absorbed after oral administration. It undergoes extensive metabolism primarily by the hepatic cytochrome P450 3A4 (CYP3A4) isoenzyme, forming active metabolites. A portion of *procainamide* is acetylated in the liver to *N*-acetylprocainamide (NAPA), which has the properties and adverse effects of a class III antiarrhythmic drug. NAPA is eliminated via the kidney; therefore, dosages of *procainamide* should be adjusted in patients with renal dysfunction. *Disopyramide* is well absorbed after oral administration and is metabolized in the liver by CYP3A4 to a less active metabolite and several inactive metabolites. About half of the drug is excreted unchanged by the kidneys.

4. Adverse effects: Due to enhanced proarrhythmic effects and ability to worsen heart failure symptoms, class IA drugs should not be used in patients with atherosclerotic heart disease or heart failure with reduced ejection fraction. Large doses of *quinidine* may induce the symptoms of cinchonism

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(blurred vision, tinnitus, headache, disorientation, and psychosis). Drug interactions are common with *quinidine* since it is an inhibitor of both CYP2D6 and P-glycoprotein. Intravenous administration of *procainamide* may cause hypotension. *Disopyramide* has the most anticholinergic adverse effects of the class IA drugs (dry mouth, urinary retention, blurred vision, and constipation). Both *quinidine* and *disopyramide* should be used with caution with potent inhibitors of CYP3A4.

B. Class IB antiarrhythmic drugs: lidocaine and mexiletine

The class IB agents rapidly associate and dissociate from Na^+ channels. Thus, the actions are greater when the cardiac cell is depolarized or firing rapidly. The class IB drugs *lidocaine* [LYE-doe-kane] and *mexiletine* [mex-IL-e-teen] are useful in treating ventricular arrhythmias.

1. Mechanism of action: In addition to Na^+ channel blockade, *lidocaine* and *mexiletine* shorten phase 3 repolarization and decrease the duration of the action potential (Figure 11.7). Neither drug contributes to negative inotropy.

POLE STAR

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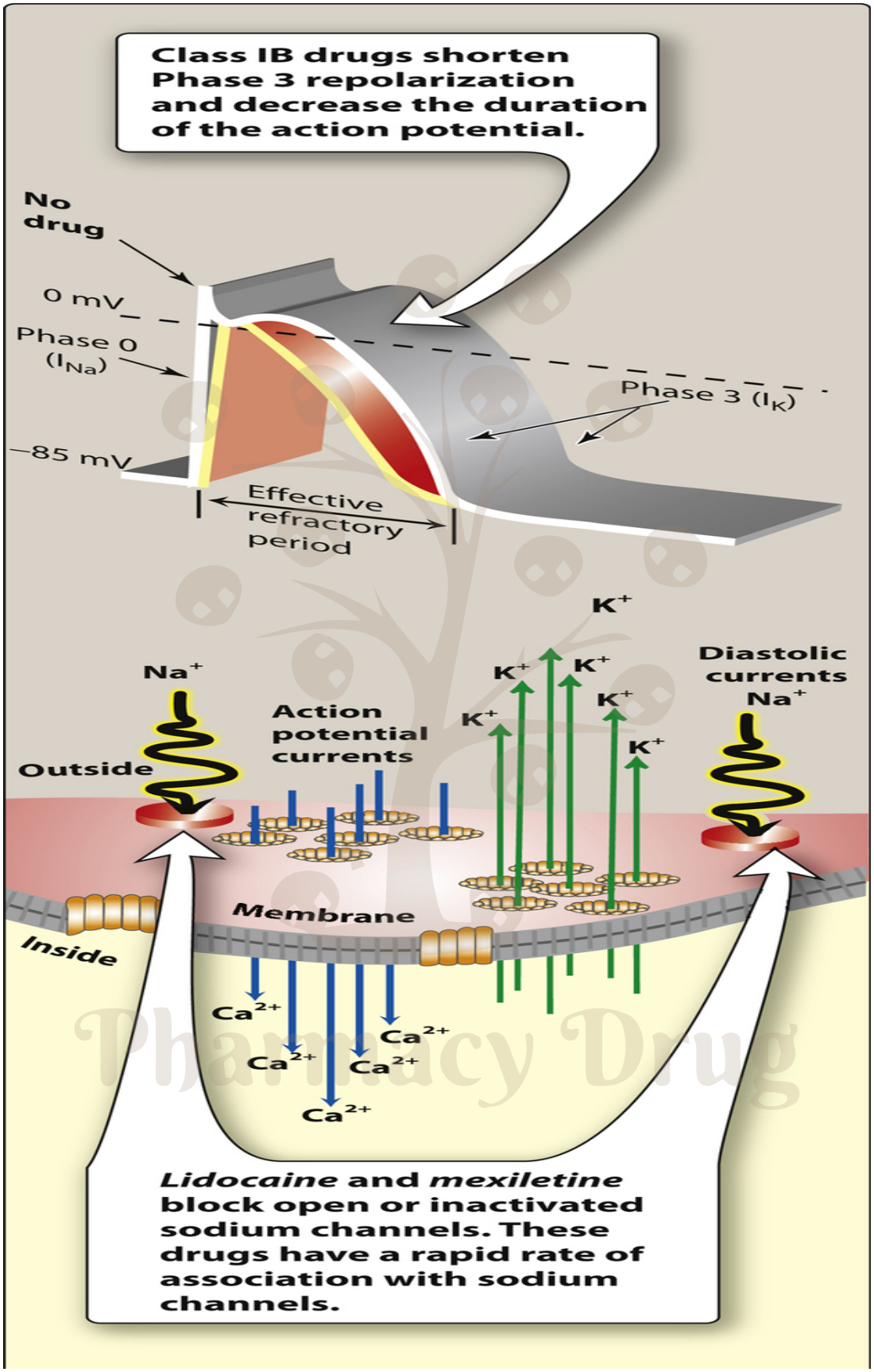

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Figure 11.7 Schematic diagram of the effects of class IB agents. I_{Na} and I_K are transmembrane currents due to the movement of Na^+ and K^+, respectively.

2. Therapeutic uses: Although *amiodarone* is the drug of choice for ventricular fibrillation or ventricular tachycardia, *lidocaine* may be used as an alternative. It may also be used in combination with *amiodarone* for ventricular tachycardia storm, which is characterized as a state of cardiac electrical instability manifesting in multiple episodes of ventricular tachycardia or fibrillation. *Lidocaine* does not markedly slow conduction and, thus, has little effect on atrial or AV junction arrhythmias. *Mexiletine* is used for chronic treatment of ventricular arrhythmias, often in combination with *amiodarone*.

3. Pharmacokinetics: *Lidocaine* is given intravenously because of extensive first-pass metabolism by the liver. The drug is dealkylated to two active metabolites, primarily by CYP1A2 with a minor role by CYP3A4. *Lidocaine* should be monitored closely when given in combination with drugs affecting these CYP isoenzymes. *Mexiletine* is well absorbed after oral administration. It is metabolized in the liver primarily by CYP2D6 to inactive metabolites and excreted mainly via the biliary route.

4. Adverse effects: *Lidocaine* has a fairly wide therapeutic index. Central nervous system (CNS) effects include nystagmus (early indicator of toxicity), drowsiness, slurred speech, paresthesia, agitation, confusion, and convulsions, which often limit the duration of continuous infusions. *Mexiletine* has a narrow therapeutic index, and caution should be used when administering the drug with inhibitors of CYP2D6. Nausea, vomiting, and dyspepsia are the most common adverse effects.

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C. Class IC antiarrhythmic drugs: flecainide and propafenone

These drugs slowly dissociate from resting Na^+ channels and show prominent effects even at normal heart rates. Due to their negative inotropic and proarrhythmic effects, use of these agents is avoided in patients with structural heart disease (left ventricular hypertrophy, heart failure, atherosclerotic heart disease).

1. Mechanism of action: *Flecainide* [FLEK-a-nide] suppresses phase 0 upstroke in Purkinje and myocardial fibers (Figure 11.8). This causes marked slowing of conduction in all cardiac tissue, with a minor effect on the duration of the action potential and refractoriness. Automaticity is reduced by an increase in the threshold potential, rather than a decrease in slope of phase 4 depolarization. *Flecainide* also blocks K^+ channels, leading to increased duration of the action potential. *Propafenone* [proe-PAF-e-none], like *flecainide*, slows conduction in all cardiac tissues but does not block K^+ channels. It possesses weak β-blocking properties.

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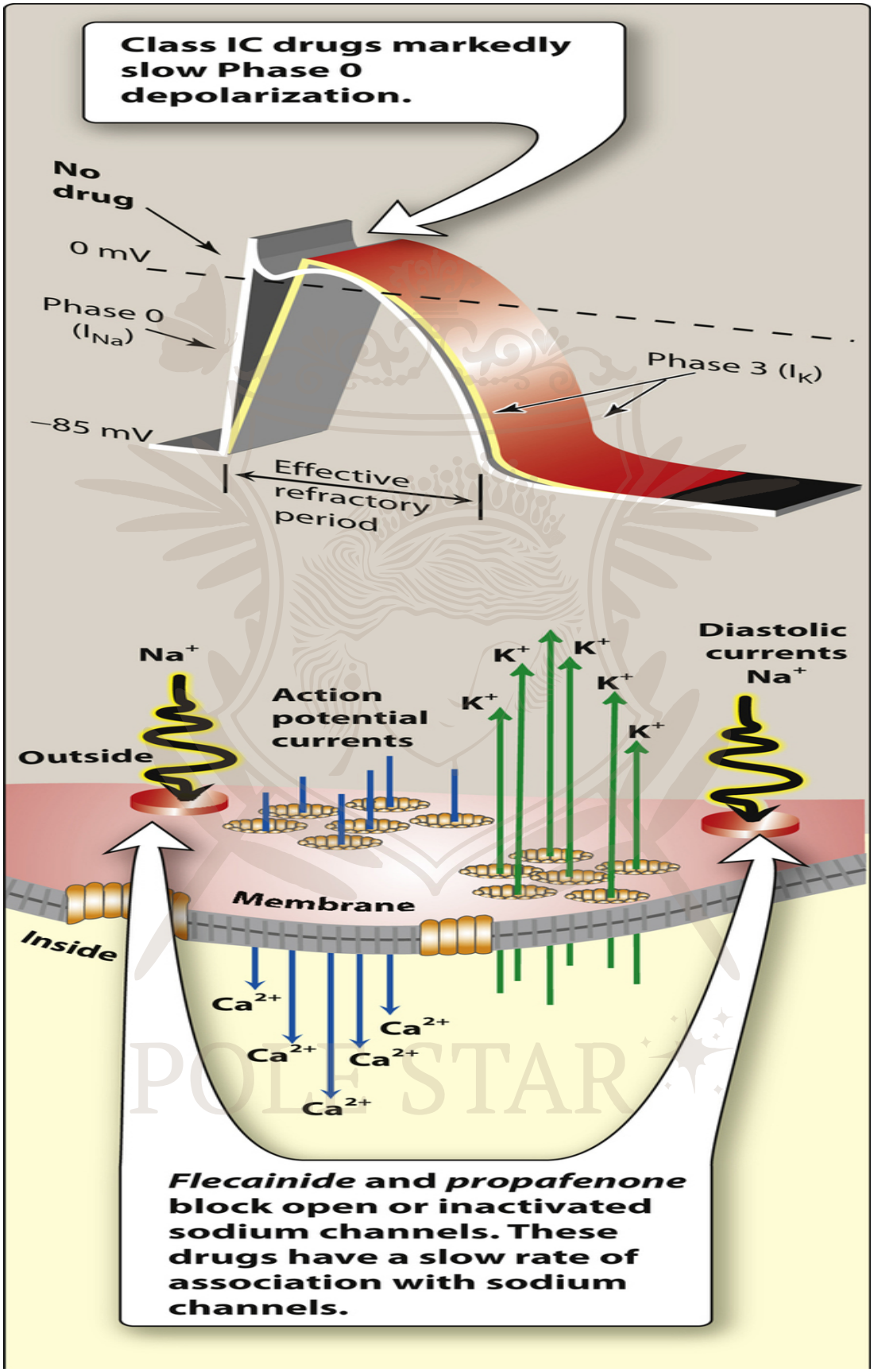
Class IC drugs markedly slow Phase 0 depolarization.
No drug
0 mV
Phase 0 (I_{Na})
Phase 3 (I_K)
−85 mV
Effective refractory period
Na^+
Outside
Action potential currents
K^+
K^+
K^+
K^+
K^+
Diastolic currents Na^+
Membrane
Inside
Ca^{2+}
Ca^{2+}
Ca^{2+}
Ca^{2+}
Ca^{2+}
Flecainide and *propafenone* block open or inactivated sodium channels. These drugs have a slow rate of association with sodium channels.

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Figure 11.8 Schematic diagram of the effects of class IC agents. I_{Na} and I_K are transmembrane currents due to the movement of Na^+ and K^+, respectively.

2. Therapeutic uses: *Flecainide* is useful in the maintenance of sinus rhythm in atrial flutter or fibrillation in patients without structural heart disease and in treating refractory ventricular arrhythmias. Use of *propafenone* is restricted mostly to atrial arrhythmias, such as rhythm control of atrial fibrillation or flutter and paroxysmal supraventricular tachycardia prophylaxis in patients with AV reentrant tachycardias.

3. Pharmacokinetics: *Flecainide* is well absorbed after oral administration and is metabolized by CYP2D6 to multiple metabolites. The parent drug and metabolites are mostly eliminated renally. *Propafenone* is metabolized to active metabolites primarily via CYP2D6 and also by CYP1A2 and CYP3A4. The metabolites are excreted in the urine and the feces.

4. Adverse effects: *Flecainide* is generally well tolerated, with blurred vision, dizziness, and nausea being the most frequent unwanted side effects. *Propafenone* has a similar side-effect profile but may also cause bronchospasm, and it should be avoided in patients with asthma. *Propafenone* is also an inhibitor of P-glycoprotein. Both drugs should be used with caution with potent inhibitors of CYP2D6.

IV. CLASS II ANTIARRHYTHMIC DRUGS

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Class II agents are β-adrenergic antagonists, or β-blockers. These drugs diminish phase 4 depolarization and, thus, depress automaticity, prolong AV conduction, and decrease heart rate and contractility. Class II agents are useful in treating tachyarrhythmias caused by increased sympathetic activity. They are also used for atrial flutter and fibrillation and for AV nodal reentrant tachycardia. In addition, β-blockers prevent life-threatening ventricular arrhythmias following a myocardial infarction.

Metoprolol [me-TOE-pro-lol] is the most widely used β-blocker for the treatment of cardiac arrhythmias. Compared with nonselective β-blockers, such as *propranolol* [pro-PRAN-oh-lol], it has a reduced risk of eliciting bronchospasm. It is extensively metabolized by CYP2D6 and has CNS penetration (less than *propranolol* but more than *atenolol* [a-TEN-oh-lol]). *Esmolol* [ES-moe-lol] is a very short-acting β-blocker used for intravenous administration in acute arrhythmias that occur during surgery or emergency situations. *Esmolol* is rapidly metabolized by esterases found in the plasma. As such, there are no pharmacokinetic drug interactions. Common adverse effects with β-blockers include bradycardia, hypotension, fatigue, and dizziness (see Chapter 7).

V. CLASS III ANTIARRHYTHMIC DRUGS

Class III agents block K^+ channels and, thus, diminish the outward K^+ current during repolarization of cardiac cells. These agents prolong the duration of the action potential without altering phase 0 of depolarization or the resting membrane potential (Figure 11.9). Instead, they prolong the effective refractory period, increasing refractoriness. All class III drugs have the potential to induce arrhythmias.

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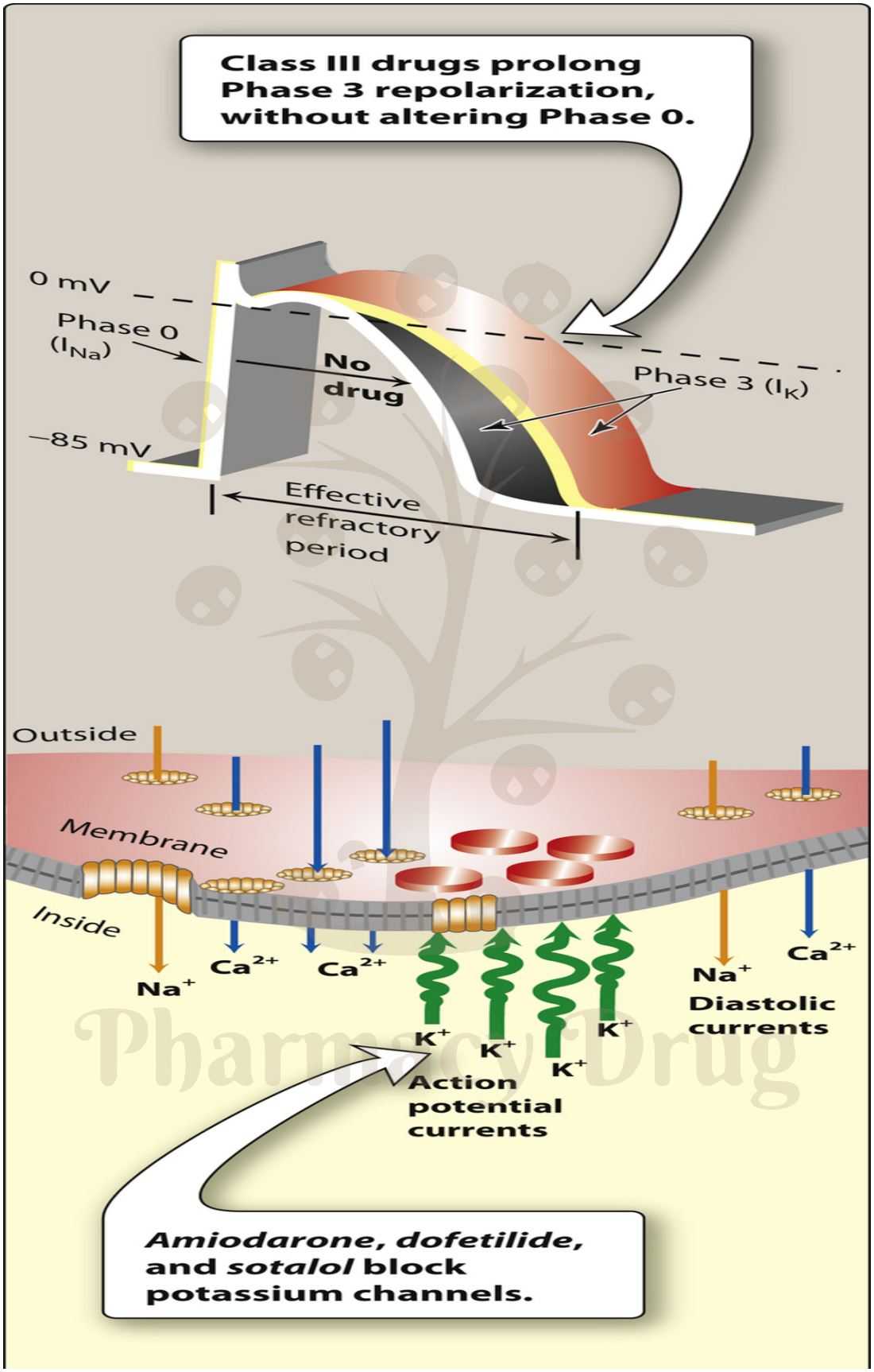

Pharmacy Drug

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Figure 11.9 Schematic diagram of the effects of class III agents. I_{Na} and I_K are transmembrane currents due to the movement of Na^+ and K^+, respectively.

A. Amiodarone

1. Mechanism of action: *Amiodarone* [a-MEE-oh-da-rone] contains iodine and is related structurally to thyroxine. It has complex effects, showing class I, II, III, and IV actions, as well as α-blocking activity. Its dominant effect is prolongation of the action potential duration and the refractory period by blocking K^+ channels.

2. Therapeutic uses: *Amiodarone* is effective in the treatment of severe refractory supraventricular and ventricular tachyarrhythmias. *Amiodarone* has been a mainstay of therapy for the rhythm management of atrial fibrillation or flutter. Despite its adverse-effect profile, *amiodarone* is thought to be the least proarrhythmic of the class I and III antiarrhythmic drugs.

3. Pharmacokinetics: *Amiodarone* is incompletely absorbed after oral administration. The drug is unusual in having a prolonged half-life of several weeks and a very large volume of distribution. Full clinical effects may not be achieved until months after initiation of treatment, unless loading doses are employed.

4. Adverse effects: *Amiodarone* shows a variety of toxic effects, including pulmonary fibrosis, neuropathy, hepatotoxicity, corneal deposits, optic neuritis, blue-gray skin discoloration, and hypo- or hyperthyroidism. However, use of low doses and close monitoring reduce toxicity, while retaining clinical efficacy. *Amiodarone* is subject to numerous drug interactions, since it is metabolized by CYP3A4 and serves as

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an inhibitor of CYP1A2, CYP2C9, CYP2D6, and P-glycoprotein.

B. Dronedarone

Dronedarone [droe-NE-da-rone] is a benzofuran *amiodarone* derivative, which is less lipophilic and has a shorter half-life than *amiodarone.* It does not have the iodine moieties that are responsible for the thyroid dysfunction associated with *amiodarone.* Like *amiodarone*, it has class I, II, III, and IV actions. *Dronedarone* has a better adverse-effect profile than does *amiodarone* but may still cause liver failure. The drug is contraindicated in those with symptomatic heart failure or permanent atrial fibrillation due to an increased risk of death. Currently, *dronedarone* is used to maintain sinus rhythm in atrial fibrillation or flutter, but it is less effective than *amiodarone*.

C. Sotalol

Sotalol [SOE-ta-lol], although a class III antiarrhythmic agent, also has nonselective β-blocker activity. The levorotatory isomer (*l -sotalol*) has β-blocking activity, and *d -sotalol* has class III antiarrhythmic action. *Sotalol* blocks a rapid outward K^+ current, known as the delayed rectifier current. This blockade prolongs both repolarization and duration of the action potential, thus lengthening the effective refractory period. *Sotalol* is used for maintenance of sinus rhythm in patients with atrial fibrillation, atrial flutter, or refractory paroxysmal supraventricular tachycardia and in the treatment of ventricular arrhythmias. Since *sotalol* has β-blocking properties, it is commonly used for these indications in patients with left ventricular hypertrophy or atherosclerotic heart disease. This drug can cause the typical adverse effects associated with β-blockers but has an overall low rate of adverse effects when compared with other antiarrhythmic drugs. The dosing interval should be extended in patients with renal disease, since the drug is renally eliminated. To reduce the risk of

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proarrhythmic effects, *sotalol* should be initiated in the hospital to monitor QT interval.

D. Dofetilide

Dofetilide [doe-FET-i-lide] is a pure K^+ channel blocker. It can be used as a first-line antiarrhythmic agent in patients with persistent atrial fibrillation and heart failure or in those with coronary artery disease. Because of the risk of proarrhythmia, *dofetilide* initiation is limited to the inpatient setting. The half-life of this oral drug is 10 hours. The drug is mainly excreted unchanged in the urine. Drugs that inhibit active tubular secretion are contraindicated with *dofetilide*.

E. Ibutilide

Ibutilide [eye-BUE-til-ide] is a K^+ channel blocker that also activates the inward Na^+ current (mixed class III and IA actions). *Ibutilide* is the drug of choice for chemical conversion of atrial flutter, but electrical cardioversion has supplanted its use. It undergoes extensive first-pass metabolism and is not used orally. Initiation is also limited to the inpatient setting due to the risk of arrhythmia.

VI. CLASS IV ANTIARRHYTHMIC DRUGS

Class IV drugs are the nondihydropyridine Ca^{2+} channel blockers *verapamil* [ver-AP-a-mil] and *diltiazem* [dil-TYE-a-zem]. Although voltage-sensitive Ca^{2+} channels occur in many different tissues, the major effect of Ca^{2+} channel blockers is on vascular smooth muscle and the heart. Both drugs show greater action on the heart than on vascular smooth muscle, but more so with *verapamil.* In the heart, *verapamil* and *diltiazem* bind only to open depolarized voltage-sensitive channels, thus decreasing the inward current carried by Ca^{2+}. These drugs are use-dependent in that they prevent

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repolarization until the drug dissociates from the channel, resulting in a decreased rate of phase 4 spontaneous depolarization. They also slow conduction in tissues that are dependent on Ca^{2+} currents, such as the AV and SA nodes (Figure 11.10). These agents are more effective against atrial arrhythmias than they are against ventricular arrhythmias. They are useful in treating reentrant supraventricular tachycardia and in reducing the ventricular rate in atrial flutter and fibrillation. Common adverse effects include bradycardia, hypotension, and peripheral edema. Both drugs are metabolized in the liver by CYP3A4. Dosage adjustments may be needed in patients with hepatic dysfunction. Both agents are subject to many drug interactions since they are CYP3A4 inhibitors, as well as substrates and inhibitors of P-glycoprotein.

Pharmacy Drug

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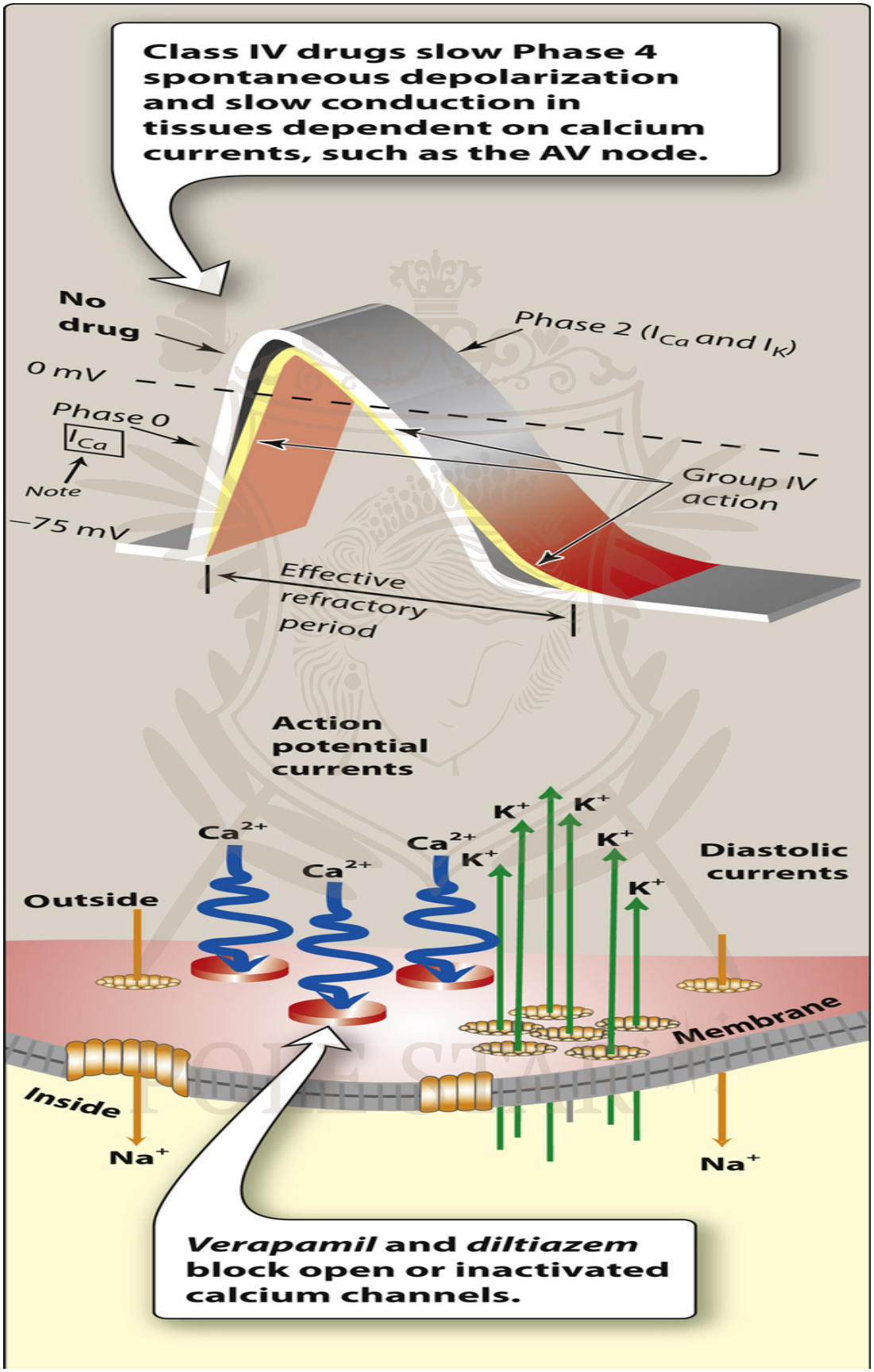
Class IV drugs slow Phase 4 spontaneous depolarization and slow conduction in tissues dependent on calcium currents, such as the AV node.
No drug
0 mV
Phase 2 (I_{Ca} and I_K)
Phase 0
I_{Ca}
Note
Group IV action
−75 mV
Effective refractory period
Action potential currents
Ca^{2+}
Ca^{2+}
Ca^{2+}
K^+
K^+
K^+
K^+
K^+
Diastolic currents
Outside
Membrane
Inside
Na^+
Na^+
Verapamil and *diltiazem* block open or inactivated calcium channels.

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Figure 11.10 Schematic diagram of the effects of class IV agents. I_{Ca} and I_K are transmembrane currents due to the movement of Ca^{2+} and K^+, respectively. AV = atrioventricular.

Clinical Application 11.1: Antiarrhythmic Drugs and Structural Heart Disease

Patients diagnosed with cardiac arrhythmias, such as atrial fibrillation, are commonly prescribed medications to obtain rate and rhythm control. Rhythm control strategies can be used to restore and maintain normal sinus rhythm, reduce symptoms of the disease, improve exercise capacity, and prevent the development of tachycardia-mediated cardiomyopathy. Due to the negative inotropic and proarrhythmic effects of certain antiarrhythmic agents, when rhythm control strategies are employed, the choice of drug therapy depends upon the presence or absence of coexisting structural heart disease. If the patient does not have structural heart disease, *dofetilide, dronedarone, flecainide, propafenone, sotalol,* or *amiodarone* are all reasonable options and recommended by current practice guidelines. For patients who have structural heart disease, treatment selection is further guided by whether the patient has left ventricular hypertrophy, coronary artery disease, or heart failure. For patients with left ventricular hypertrophy (myocardial wall thickness greater than 1.5 cm), *amiodarone* is considered the safest option. For coronary artery disease, *dofetilide, dronedarone, sotalol,* or *amiodarone* are appropriate options. Finally, in patients with heart failure with reduced ejection fraction, *amiodarone* or *dofetilide* should be utilized.

VII. OTHER ANTIARRHYTHMIC DRUGS

A. Digoxin

Digoxin [di-JOX-in] inhibits the Na^+/K^+-ATPase pump, ultimately shortening the refractory period in atrial and ventricular myocardial cells while prolonging the effective refractory period

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and diminishing conduction velocity in the AV node. *Digoxin* is used to control ventricular response rate in atrial fibrillation and flutter; however, sympathetic stimulation easily overcomes the inhibitory effects of *digoxin.* At toxic concentrations, *digoxin* causes ectopic ventricular beats that may result in ventricular tachycardia and fibrillation. [Note: Serum trough concentrations of 1.0-2.0 ng/mL are desirable for atrial fibrillation or flutter, whereas lower concentrations of 0.5-0.9 ng/mL are targeted for heart failure with reduced ejection fraction.]

Clinical Application 11.2: Digoxin Toxicity

While therapeutic levels of *digoxin* are effective in aiding in the control of certain arrhythmias, *digoxin* toxicity is also a concern and can cause other life-threatening arrhythmias. Therefore, when *digoxin* is initiated to treat arrhythmias, serum concentrations should be measured upon initiation of the drug, with any changes in renal function or electrolytes, if toxicity is suspected, and following dose changes. Of note, these levels are drawn more frequently if *digoxin* is being used to treat heart failure. The risk for *digoxin* toxicity is higher in patients with electrolyte abnormalities (such as hypokalemia or hypomagnesemia) or decreased renal function. Additionally, concomitant use of p-glycoprotein inducers or inhibitors, diuretics, and antacids can affect *digoxin* serum concentrations. Common symptoms of *digoxin* toxicity include bradycardia, tachycardia, nausea/vomiting, vision changes (blurred or yellow vision), confusion, and loss of appetite. Concomitant hyperkalemia is common with acute *digoxin* toxicity, and higher levels of *digoxin* indicate higher risk of death. While signs of toxicity may occur at lower *digoxin* levels, it is thought that this risk is particularly higher with serum levels greater than 2.0 ng/mL. When measuring *digoxin* serum concentrations, they should be measured at steady state (at least 6 hours after administration of the last dose or 12 to 24 hours in patients with advanced kidney disease). If *digoxin* toxicity is confirmed, *digoxin* should be discontinued and *digoxin* antidotes can be administered.

B. Adenosine

Adenosine [ah-DEN-oh-seen] is a naturally occurring nucleoside, but at high doses, the drug decreases conduction velocity, prolongs the refractory period, and decreases automaticity in the AV node. Intravenous *adenosine* is the drug of choice for

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converting acute supraventricular tachycardias. It has low toxicity but causes flushing, chest pain, and hypotension. *Adenosine* has an extremely short duration of action (approximately 10-15 seconds) due to rapid uptake by erythrocytes and endothelial cells.

C. Magnesium sulfate

Magnesium is necessary for the transport of Na^+, Ca^{2+}, and K^+ across cell membranes. It slows the rate of SA node impulse formation and prolongs conduction time along the myocardial tissue. Intravenous *magnesium sulfate* is the salt used to treat arrhythmias, as oral *magnesium* is not effective in the setting of arrhythmia. Most notably, *magnesium* is the drug of choice for treating the potentially fatal arrhythmia torsades de pointes and *digoxin*-induced arrhythmias.

D. Ranolazine

Ranolazine [ra-NOE-la-zeen] is an antianginal drug with antiarrhythmic properties similar to *amiodarone.* However, its main effect is to shorten repolarization and decrease the action potential duration, similar to *mexiletine.* It is used to treat refractory atrial and ventricular arrhythmias, often in combination with other antiarrhythmic drugs. It is well tolerated, with dizziness and constipation as the most common adverse effects. *Ranolazine* is extensively metabolized in the liver by CYP3A and CYP2D6 isoenzymes and is mainly excreted by the kidney. Concomitant use with strong CYP3A inducers or inhibitors is contraindicated.

Pharmacy Drug

Chapter Summary

- Arrhythmias occur when there is either a deviation from normal impulse generation (abnormal automaticity) or a defect in impulse conduction in the myocardium.
- Antiarrhythmic drugs are used to help prevent arrhythmias or reduce symptoms of arrhythmias.

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- Antiarrhythmic drugs do not come without side effects, the most dangerous one being their proarrhythmic actions. Thus, QT intervals should be monitored and caution should be employed when other QT-prolonging drugs are used concomitantly with antiarrhythmic agents.
- Antiarrhythmic drugs are classified into four "classes" using the Vaughan–Williams classification system, which groups them based on their predominant effects on the action potential.
- Due to the proarrhythmic effects and/or negative inotropic effects of some of these agents, a history of structural heart disease (left ventricular hypertrophy, heart failure, or atherosclerotic heart disease) must be considered when choosing an antiarrhythmic drug. In patients with heart failure and concomitant atrial fibrillation or flutter, *amiodarone* or *dofetilide* are used. *Amiodarone* is considered the most effective antiarrhythmic drug, since it possesses many antiarrhythmic mechanisms.
- *Flecainide* and *propafenone* are well tolerated and are commonly used for rhythm control of atrial fibrillation or flutter. However, both should be avoided in patients with structural heart disease.
- β-Blockers slow heart rate by directly antagonizing β1 receptors in the SA and AV nodes. Non-dihydropyridine calcium channel blockers also slow heart rate by blocking calcium channels in the SA and AV nodes.

STUDY QUESTIONS

Choose the ONE best answer.

11.1A 60-year-old woman had a myocardial infarction. Which agent should be used to prevent life-threatening arrhythmias that can occur post myocardial infarction in this patient?

A. Digoxin
B. Flecainide
C. Metoprolol
D. Procainamide

Correct answer = C. β-Blockers such as metoprolol prevent arrhythmias that occur subsequent to a myocardial infarction. None of the other drugs has been shown to be effective in preventing postinfarct arrhythmias. Flecainide should be avoided in patients with structural heart disease.

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11.2A 57-year-old man is being treated for an atrial arrhythmia. He complains of dry mouth, blurred vision, and urinary hesitancy. Which antiarrhythmic drug is he mostly like taking?

A. Metoprolol
B. Disopyramide
C. Dronedarone
D. Sotalol

Correct answer = B. The clustered symptoms of dry mouth, blurred vision, and urinary hesitancy are characteristic of anticholinergic adverse effects, which are caused by class IA agents (in this case, disopyramide). The other drugs do not cause anticholinergic effects.

11.3A 78-year-old woman has been newly diagnosed with atrial fibrillation. She is not currently having symptoms of palpitations or fatigue. Which of the following is appropriate to initiate for rate control as an outpatient?

A. Dronedarone
B. Esmolol
C. Flecainide
D. Metoprolol

Correct answer = D. Only B and D are options to control rate. The other options are used for rhythm control in patients with atrial fibrillation. Since esmolol is intravenous only, the only option to start as an outpatient is metoprolol.

11.4All of the following are adverse effects of amiodarone except:

A. Cinchonism
B. Hypothyroidism
C. Pulmonary fibrosis
D. Blue skin discoloration

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Correct answer = A. Cinchonism is a constellation of symptoms (blurred vision, tinnitus, headache, psychosis) that is known to occur with quinidine. All other options are adverse effects with amiodarone that require close monitoring.

11.5Which arrhythmia can be treated with lidocaine?

A. Paroxysmal supraventricular ventricular tachycardia
B. Atrial fibrillation
C. Atrial flutter
D. Ventricular tachycardia

Correct answer = D. Lidocaine has little effect on atrial or AV nodal tissue; thus, it used for ventricular arrhythmias such as ventricular tachycardia.

11.6A clinician would like to initiate a drug for rhythm control of atrial fibrillation. Which of the following coexisting conditions would allow for initiation of flecainide?

A. Hypertension
B. Left ventricular hypertrophy
C. Coronary artery disease
D. Heart failure

Correct answer = A. Since flecainide can increase the risk of sudden cardiac death in those with a history of structural heart disease, only coexisting hypertension will allow for flecainide initiation. Structural heart disease includes left ventricular hypertrophy, heart failure, and atherosclerotic heart disease.

11.7An ECG on a 57-year-old man exhibits torsades de pointes. Which drug is the drug of choice for treating this fatal arrhythmia?

A. Amiodarone
B. Magnesium sulfate
C. Quinidine
D. Magnesium citrate

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Correct answer = B. Intravenous magnesium sulfate is the drug of choice for treating torsades de pointes. Magnesium citrate is a laxative. Amiodarone and quinidine could potentially worsen torsades de pointe.

11.8 Which of the following class III antiarrhythmic drugs can be initiated in an outpatient setting without QT monitoring?

A. Dofetilide
B. Sotalol
C. Metoprolol
D. Amiodarone

Correct answer = D. Amiodarone does not require QT monitoring upon initiation. It is recommended that dofetilide and sotalol be initiated in the hospital to reduce the risk of proarrhythmic effects. While metoprolol can be initiated in an outpatient setting, it is not a class III agent.

11.9 A 62-year-old man is complaining of peripheral edema. Which of the following medications is most likely contributing to this?

A. Sotalol
B. Digoxin
C. Verapamil
D. Atenolol

Correct answer = C. One side effect of verapamil is peripheral edema.

11.10 Propafenone should be avoided in all of the following concomitant disease states except:

A. Diabetes
B. Heart failure
C. Asthma
D. Coronary artery disease

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Correct answer = A. Propafenone should be avoided in patients with structural heart disease (for example, left ventricular hypertrophy, heart failure, and coronary artery disease) due to its negative inotropic and proarrhythmic effects. Additionally, it may cause bronchospasms and should be avoided in patients with asthma.

POLE STAR

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12

Antianginal Drugs

Kristyn M. Pardo

I. OVERVIEW

Atherosclerotic disease of the coronary arteries, also known as coronary artery disease (CAD) or ischemic heart disease (IHD), is the most common cause of mortality worldwide. Atherosclerotic lesions in coronary arteries can obstruct blood flow, leading to an imbalance in myocardial oxygen supply and demand that presents as stable angina or an acute coronary syndrome (myocardial infarction [MI] or unstable angina). Spasms of vascular smooth muscle may also impede cardiac blood flow, reducing perfusion and causing ischemia and angina pain. Typical angina pectoris or “angina” is a characteristic sudden, severe, crushing chest pain that may radiate to the left neck, jaw, and arm. All patients with IHD and angina should receive guideline-directed medical therapy with emphasis on lifestyle modifications (smoking cessation, physical activity, weight management) and management of modifiable risk factors (hypertension, diabetes, dyslipidemia) to reduce cardiovascular morbidity and mortality. Medications used for the management of stable angina are summarized in Figure 12.1.

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β-BLOCKERS (NONSELECTIVE)

Nadolol CORGARD
Propranolol INDERAL, INNOPRAN XL
Sotalol BETAPACE, SORINE

β1-BLOCKERS (CARDIOSELECTIVE)

Atenolol TENORMIN
Bisoprolol GENERIC ONLY
Metoprolol LOPRESSOR, TOPROL-XL
Nebivolol BYSTOLIC

CALCIUM CHANNEL BLOCKERS (DIHYDROPYRIDINES)

Amlodipine NORVASC
Felodipine PLENDIL
Nifedipine ADALAT, PROCARDIA

CALCIUM CHANNEL BLOCKERS (NONDIHYDROPYRIDINE)

Diltiazem CARDIZEM, CARTIA, TIAZAC
Verapamil CALAN, VERELAN

NITRATES

Nitroglycerin MINITRAN, NITRO-DUR, NITROSTAT
Isosorbide dinitrate DILATRATE-SR, ISORDIL
Isosorbide mononitrate GENERIC ONLY

SODIUM CHANNEL BLOCKER

Ranolazine RANEXA

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Figure 12.1 Summary of antianginal drugs.

Clinical Application 12.1: Coronary Artery Disease—Options Other Than Medication

Coronary artery disease extent and severity can be assessed by stress testing, cardiac imaging, and angiography. Revascularization or percutaneous coronary interventions can benefit certain patients, such as those with severe ischemic heart disease or patients with persistent angina symptoms that negatively impact quality of life despite optimal medical therapy.

II. TYPES OF ANGINA

Angina pectoris has three patterns: (1) stable, which is effort-induced and the classic or typical angina; (2) unstable angina; and (3) Prinzmetal, which is the variant subtype that can be vasospastic or a resting angina. The different types of angina are caused by varying combinations of increased myocardial oxygen demand and decreased myocardial perfusion.

A. Stable angina, effort-induced angina, classic or typical angina

Classic or typical angina pectoris is the most common form of angina. It is usually characterized by a short-lasting burning, heavy, or squeezing feeling in the chest. Some ischemic episodes may present "atypically"—with extreme fatigue, nausea, or diaphoresis—while others may not be associated with any symptoms (silent angina). Atypical presentations are more common in women, diabetic patients, and the elderly.

Atherosclerotic lesions can reduce blood flow in the coronary arteries. Classic angina is caused by the reduction of coronary perfusion due to a fixed obstruction (atherosclerotic lesion) within a coronary artery. Increased myocardial oxygen demand, such as

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that produced by physical activity, emotional stress or excitement, or any other cause of increased cardiac workload (Figure 12.2), may induce ischemia. Typical angina pectoris can be promptly relieved by rest or *nitroglycerin* [nye-troe-GLIS-er-in]. When the pattern of chest pain and the amount of effort needed to trigger the chest pain does not vary over time, the angina is named "stable angina."

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Figure 12.2 Blood flow in a coronary artery partially blocked with atherosclerotic plaques.

B. Unstable angina

Unstable angina is chest pain that occurs with increased frequency, duration, and intensity and can be precipitated by progressively less effort. Any episode of rest angina longer than 20 minutes, any new-onset angina, any increasing (crescendo) angina, or even sudden development of shortness of breath is suggestive of unstable angina. The symptoms are not relieved by rest or *nitroglycerin.* Unstable angina is a form of acute coronary syndrome and requires hospital admission and more aggressive therapy to prevent progression to MI and death.

C. Prinzmetal, variant, vasospastic, or rest angina

Prinzmetal angina is an uncommon pattern of episodic angina that occurs at rest and is due to decreased blood flow to the heart muscle caused by spasm of the coronary arteries. Although individuals with this form of angina may have significant coronary atherosclerosis, the angina attacks are unrelated to physical activity, heart rate, or blood pressure. Prinzmetal angina generally responds promptly to coronary vasodilators, such as *nitroglycerin* and calcium channel blockers.

D. Acute coronary syndrome

Acute coronary syndrome is an emergency that results from rupture of an atherosclerotic plaque, which produces partial or complete thrombosis of a coronary artery. If the thrombus occludes most of the blood vessel, and if the occlusion is untreated, necrosis of the cardiac muscle may ensue. MI (necrosis) is typified by increases in the serum levels of biomarkers such as troponins and creatine kinase. An acute coronary syndrome may present as various electrocardiogram (ECG) changes such as ST-segment elevation myocardial

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infarction or non–ST-segment elevation myocardial infarction, or simply as unstable angina. [Note: In unstable angina, increases in biomarkers of myocardial necrosis are not necessarily present.]

III. TREATMENT STRATEGIES

Four types of drugs, used either alone or in combination, are commonly used to manage patients with stable angina: β-blockers, calcium channel blockers, organic nitrates, and the sodium channel–blocking agent *ranolazine* (Figure 12.1). These agents help to balance the cardiac oxygen supply and demand equation by affecting blood pressure, venous return, heart rate, and contractility. Figure 12.3 provides a general treatment algorithm for patients with stable angina, and Figure 12.4 summarizes angina treatment recommendations in patients with concomitant diseases.

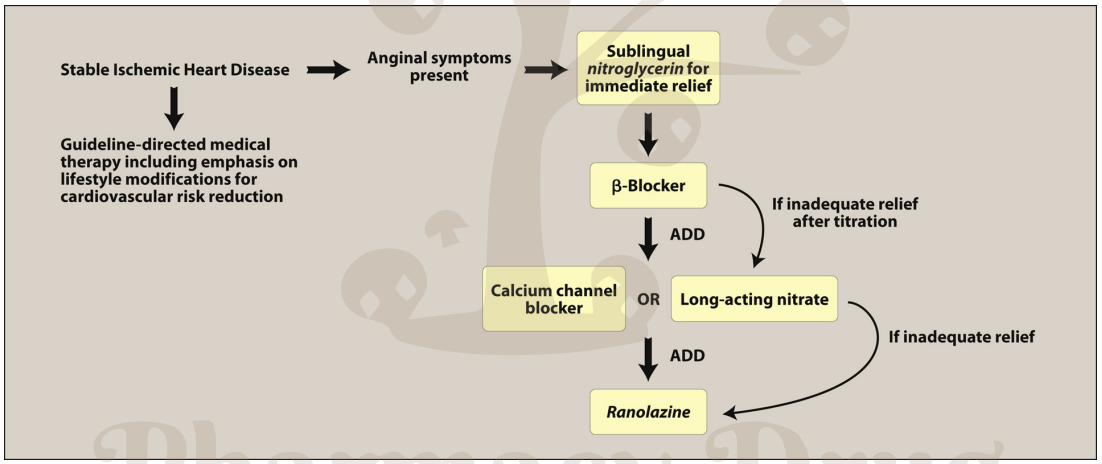

Figure 12.3 General treatment algorithm for improving symptoms in patients with stable angina.

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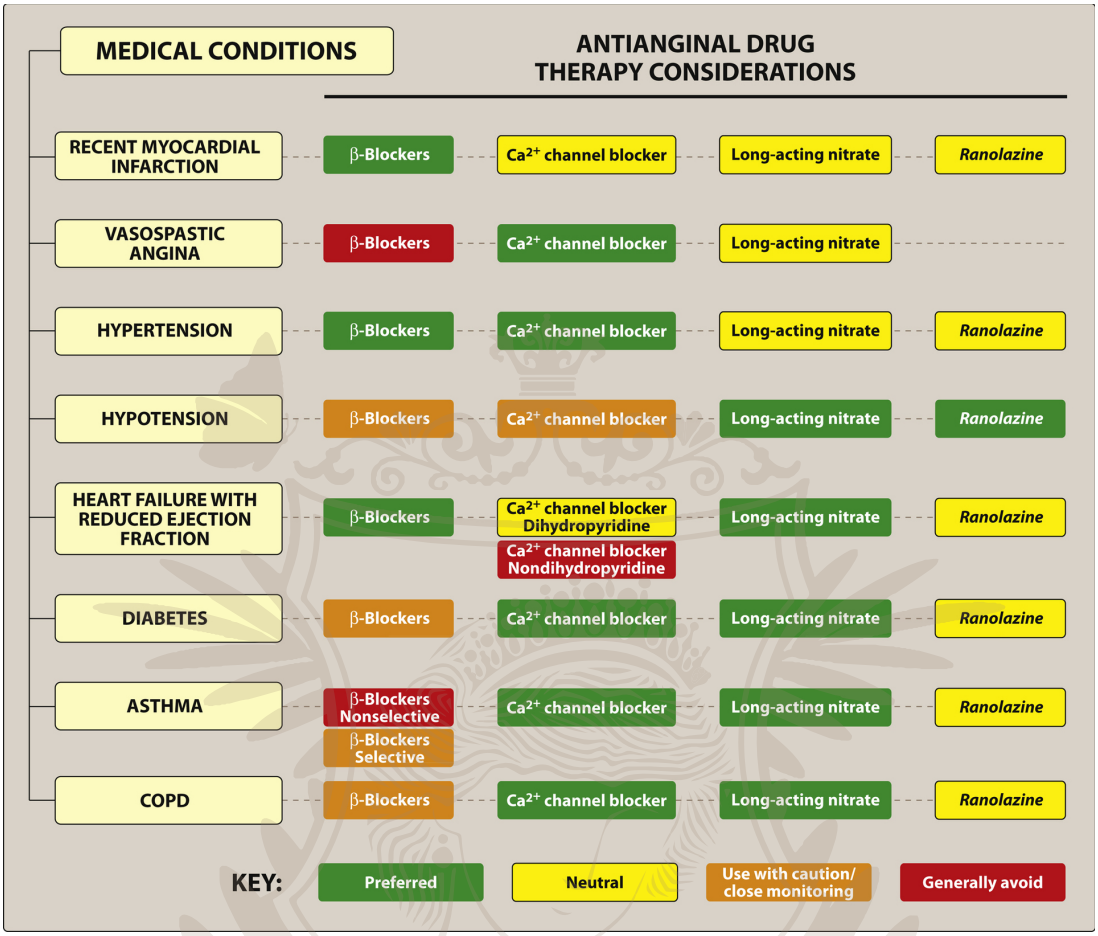

Figure 12.4 Treatment of angina in patients with concomitant diseases.COPD = chronic obstructive pulmonary disease. Key = Green – Preferred; Yellow – Neutral; Orange – Use with caution/close monitoring; Red – Generally avoid.

IV. B-ADRENERGIC BLOCKERS

The β-adrenergic blockers decrease the oxygen demands of the myocardium by blocking β_1 receptors, resulting in decreased heart rate and contractility, which subsequently decreases cardiac output and blood pressure. These agents reduce myocardial oxygen demand during exertion and at rest. As such, they can reduce both the frequency and severity of angina attacks. β-Blockers can be

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used to increase exercise duration and tolerance in patients with effort-induced angina.

β-Blockers are recommended as first-line antianginal therapy in all patients unless specifically contraindicated. The exception to this rule is vasospastic angina, in which β-blockers are ineffective and may actually worsen symptoms. β-Blockers reduce the risk of death and MI in patients who have had a prior MI and also improve mortality in patients with heart failure with reduced ejection fraction.

Propranolol is the prototype for this class of compounds; however, it acts at both β_1 and β_2 receptors and is not cardioselective (see Chapter 7). Thus, cardioselective β-blockers that only block β_1 receptors, such as *metoprolol* and *atenolol*, are preferred. [Note: All β-blockers are nonselective at high doses and can inhibit β_2 receptors.] Some newer-generation β-blockers also demonstrate α-blocking effects (for example, *carvedilol*, *labetalol*). [Note: Agents with intrinsic sympathomimetic activity (ISA) such as *pindolol* should be avoided in patients with angina and those with a history of MI.] β-Blockers should be avoided in patients with bradycardia; however, they can be used in patients with peripheral vascular disease or chronic obstructive pulmonary disease as long as they are monitored closely. Nonselective β-blockers should be avoided in patients with asthma because they may result in bronchoconstriction from β_2 blockade. β-Blockers can be used in patients with diabetes, but they may mask some of the cardinal symptoms of hypoglycemia. It is important not to discontinue β-blocker therapy abruptly. These agents should be gradually tapered off over 2 to 3 weeks to avoid rebound angina, MI, and hypertension.

Clinical Application 12.2: β-Blockers and Hypoglycemia

Many medications for diabetes increase the risk for hypoglycemia (see Chapter 24). Low blood sugar levels trigger the release of epinephrine, which produces the autonomic symptoms of hypoglycemia including tremor, palpitations, anxiety, and diaphoresis. β-Blockers can block the effects of epinephrine on adrenergic receptors. Patients with diabetes who receive β-blockers should be counseled

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to monitor carefully for diaphoresis as this may be their only autonomic indicator of a hypoglycemic episode (mediated by activation of the cholinergic system). Patients with longstanding diabetes, those treated to aggressive glucose-lowering targets, and those with history of frequent hypoglycemic episodes are at higher risk for hypoglycemia unawareness.

V. CALCIUM CHANNEL BLOCKERS

Calcium is essential for muscular contraction. Calcium influx is increased in ischemia because of the membrane depolarization that hypoxia produces. In turn, this promotes the activity of several ATP-consuming enzymes, thereby depleting energy stores and worsening the ischemia. The calcium channel blockers protect the tissue by inhibiting the entrance of calcium into cardiac and smooth muscle cells of the coronary and systemic arterial beds. All calcium channel blockers are, therefore, arteriolar vasodilators that decrease smooth muscle tone and vascular resistance. These agents primarily affect the resistance of peripheral and coronary arteriolar smooth muscle. In the treatment of effort-induced angina, calcium channel blockers reduce myocardial oxygen consumption by decreasing vascular resistance, thereby decreasing afterload. Their efficacy in vasospastic angina is due to relaxation of the coronary arteries. All calcium channel blockers lower blood pressure.

A. Dihydropyridine calcium channel blockers

Amlodipine [am-LOE-di-peen], an oral dihydropyridine, has minimal effect on cardiac conduction and functions mainly as an arteriolar vasodilator. The vasodilatory effect of *amlodipine* is useful in the treatment of variant angina caused by spontaneous coronary spasm. *Nifedipine* [ni-FED-i-pine] is another agent in this class; it is administered as an extended-release oral formulation. [Note: Short-acting dihydropyridines should be avoided in CAD because of evidence of increased mortality after an MI and an increase in acute MI in hypertensive patients.]

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B. Nondihydropyridine calcium channel blockers

Verapamil [ver-AP-a-mil] slows atrioventricular (AV) conduction (dromotropy) directly and decreases heart rate (chronotropy) and contractility (inotropy), which all decrease blood pressure and the corresponding oxygen demand. *Verapamil* has greater negative inotropic effects than *amlodipine*, but it is a weaker vasodilator. *Verapamil* is contraindicated in patients with preexisting AV conduction abnormalities. *Diltiazem* [dil-TYE-a-zem] slows AV conduction, decreases the rate of firing from the sinus node pacemaker, and is also a coronary artery vasodilator. *Diltiazem* can relieve coronary artery spasm and is particularly useful in patients with variant angina. Nondihydropyridine calcium channel blockers can worsen heart failure in patients with reduced ejection fraction due to their negative inotropic effect; therefore, their use should be avoided in this population.

VI. ORGANIC NITRATES

These compounds cause a reduction in myocardial oxygen demand, followed by relief of symptoms. They are effective in stable, unstable, and variant angina.

A. Mechanism of action

Organic nitrates relax vascular smooth muscle by their intracellular conversion to nitric oxide, which activates guanylate cyclase and increases synthesis of cyclic guanosine monophosphate (cGMP). Elevated cGMP leads to dephosphorylation of the myosin light chain, resulting in vascular smooth muscle relaxation (Figure 12.5). Nitrates such as *nitroglycerin* cause dilation of the large veins, which reduces preload (venous return to the heart) and, therefore, reduces myocardial oxygen demand. Nitrates also dilate the coronary vasculature, providing an increased blood supply to the heart muscle.

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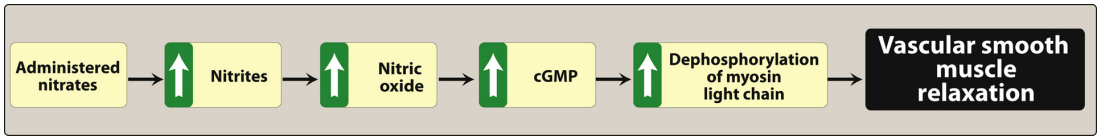

Figure 12.5 Effects of nitrates and nitrites on smooth muscle.cGMP = cyclic guanosine 3′, 5′-monophosphate.

B. Pharmacokinetics

Nitrates differ in their onset of action and rate of elimination. The onset of action varies from 1 minute for *nitroglycerin* to 30 minutes for *isosorbide* [eye-soe-SOR-bide] *mononitrate* (Figure 12.6). Significant first-pass metabolism of *nitroglycerin* occurs in the liver. Therefore, it is commonly administered via the sublingual or transdermal route (patch or ointment). Sublingual *nitroglycerin*, available in tablet or spray formulation, is the drug of choice for prompt relief of an angina attack precipitated by exercise or emotional stress. All patients should have *nitroglycerin* on hand to treat acute angina attacks. *Isosorbide mononitrate* owes its improved bioavailability and long duration of action to its stability against hepatic breakdown.

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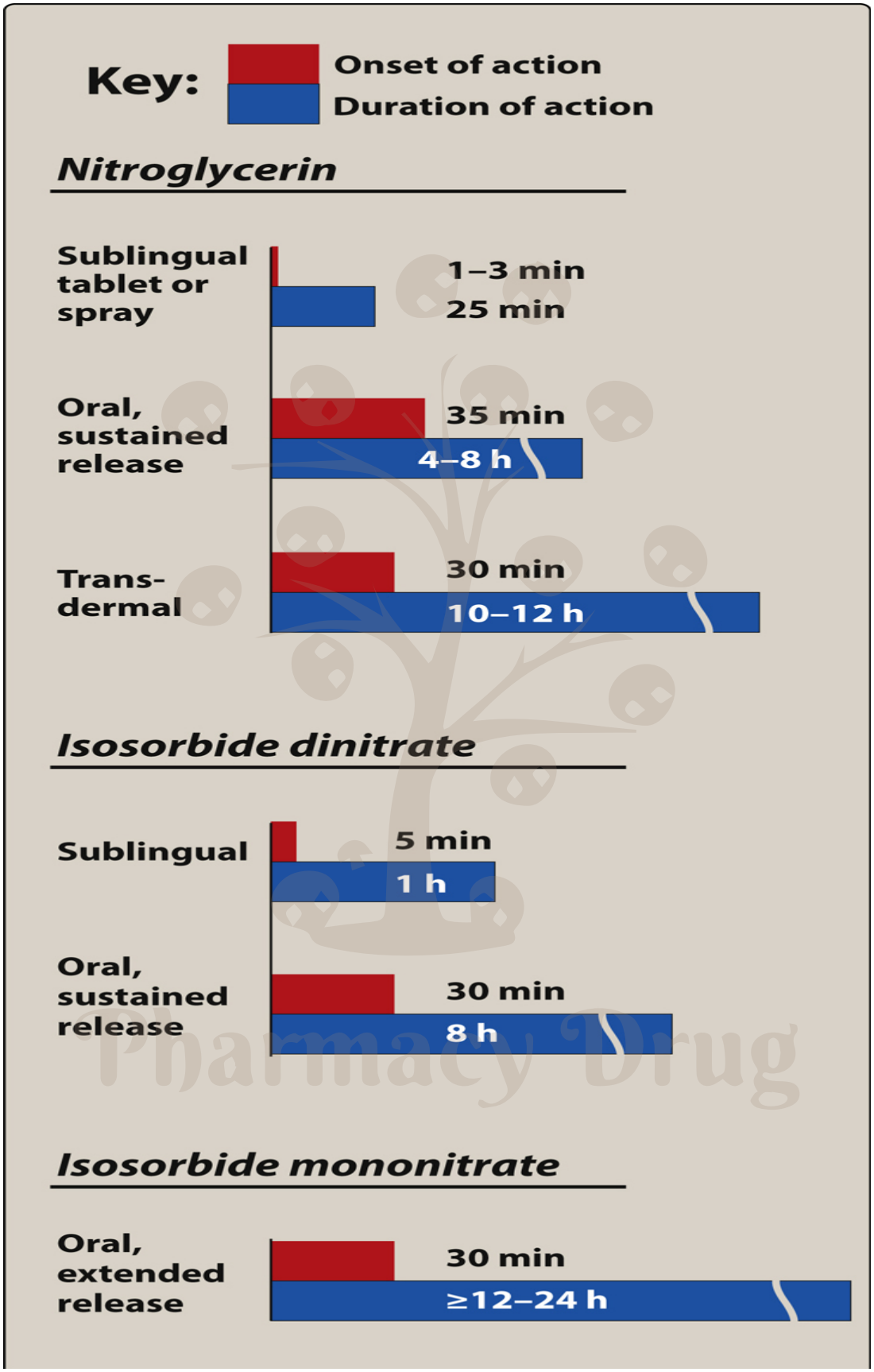

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Figure 12.6 Time to peak effect and duration of action for some common organic nitrate preparations.

C. Adverse effects

Headache is the most common adverse effect of nitrates. High doses of nitrates can also cause postural hypotension, facial flushing, and tachycardia. Phosphodiesterase type 5 inhibitors such as *sildenafil* potentiate the action of the nitrates. To preclude the dangerous hypotension that may occur, this combination is contraindicated.

Tolerance to the actions of nitrates develops rapidly as the blood vessels become desensitized to vasodilation. Tolerance can be overcome by providing a daily "nitrate-free interval" to restore sensitivity to the drug. The nitrate-free interval of 10 to 12 hours is usually provided overnight when myocardial oxygen demand is decreased (for example, patients take the last dose in late afternoon or early evening and then do not take another dose until early morning). *Nitroglycerin* patches are worn for 12 hours and then removed for 12 hours to provide the nitrate-free interval. However, variant angina worsens early in the morning, perhaps due to circadian catecholamine surges. Therefore, the nitrate-free interval in patients with variant angina should occur in the late afternoon, rather than overnight.

VII. SODIUM CHANNEL BLOCKER

Ranolazine [ra-NOE-la-zeen] inhibits the late phase of the sodium current (late I_{Na}), improving the oxygen supply and demand equation. Inhibition of late I_{Na} reduces intracellular sodium and calcium overload, thereby improving diastolic function (lusitropy). *Ranolazine* has antianginal as well as antiarrhythmic properties (see Chapter 11). It is most often used in patients who have failed other

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antianginal therapies. The antianginal effects of *ranolazine* are considerably less in women than in men. The reason for this difference in effect is unknown. *Ranolazine* is extensively metabolized in the liver, mainly by the CYP3A family and also by CYP2D6. It is also a substrate of P-glycoprotein. As such, *ranolazine* is subject to numerous drug interactions. In addition, *ranolazine* can prolong the QT interval and should be avoided with other drugs that cause QT prolongation.

Figure 12.7 provides a summary of characteristics of the antianginal drugs.

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DRUG CLASS	COMMON ADVERSE EFFECTS	DRUG INTERACTIONS	NOTES
β-Blockers *atenolol* *metoprolol* *propranolol*	Bradycardia, fatigue, sleep disturbance, depression; may blunt hypoglycemia awareness, inhibit β_2-mediated broncho-dilation in asthmatics and worsen claudication symptoms in peripheral vascular disease	β_2 Agonists (blunted effect); non-dihydropyridine calcium channel blockers (additive effects)	β_1-Selective agents preferred (*atenolol, metoprolol*). Avoid agents with ISA for angina therapy (*pindolol*)
Dihydropyridine calcium channel blockers *amlodipine* *felodipine* *nifedipine*	Peripheral edema, headache, flushing, rebound tachycardia (immediate-release formulations), hypotension	CYP 3A4 substrates (will increase drug concentrations)	Use extended-release formulations (short-acting agents can worsen angina)
Nondihydropyridine calcium channel blockers *diltiazem* *verapamil*	Bradycardia, constipation, heart failure exacerbations, gingival hyperplasia (*verapamil*), edema (*diltiazem*)	CYP 3A4 substrates (will increase drug concentrations); may increase *digoxin* levels; β-blockers and other drugs affecting AV node conduction (additive effects)	Avoid in patients with heart failure with reduced ejection fraction Extensively metabolized by liver; use caution and adjust dose accordingly in patients with cirrhosis
Organic nitrates *isosorbide dinitrate* *isosorbide mononitrate* *nitroglycerin*	Headache, hypotension, flushing, tachycardia	Contraindicated with PDE5 inhibitors (*sildenafil* and others)	Ensure nitrate-free interval to prevent tolerance
Sodium-channel inhibitor *ranolazine*	Constipation, headache, edema, dizziness, QT interval prolongation	Avoid use with CYP3A4 inducers (*phenytoin, carbamazepine, St. John's wort*) and strong inhibitors (*clarithromycin*, azole antifungals) and agents that prolong QT interval (*citalopram, quetiapine*, others). Also subject to interactions with drugs that affect CYP2D6 and p-glycoprotein.	No effect on hemodynamic parameters

Figure 12.7 Summary of characteristics of antianginal drugs.CYP = cytochrome P450; ISA = intrinsic sympathomimetic activity; PDE5 = phosphodiesterase type 5.

Clinical Application 12.3: Selection of Antianginal Therapy

All patients should be considered for *nitroglycerin* therapy during acute anginal attacks, and most patients should be prescribed β-blockers as first-line antianginal therapy. If symptoms persist despite adequate β-blocker titration, or if adverse effects require discontinuation, a calcium channel blocker, long-acting nitrate, or *ranolazine* can be considered. Choosing the best therapy requires consideration of concomitant medical conditions and medications (to assess for potential drug interactions with *ranolazine*). A calcium channel blocker such as *amlodipine* can be dually beneficial if the patient has uncontrolled hypertension. Patients with heart failure with reduced ejection fraction should not be treated with nondihydropyridine calcium channel blockers due to their negative inotropic effects. If blood pressure is well controlled or relatively low, a long-acting nitrate

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or *ranolazine* might be considered instead, as these generally do not have significant blood pressure–lowering effects.

Chapter Summary

- Coronary artery disease or ischemic heart disease is a major cause of morbidity and mortality. All patients with ischemic heart disease should receive guideline-directed medical therapy, including lifestyle modifications and management of modifiable risk factors.
- An imbalance in myocardial oxygen supply and demand results in angina. This can be caused by obstruction of blood flow (atherosclerosis) or vasospasm. Typical angina presents as sudden, severe, crushing chest pain, but atypical presentations (fatigue, nausea, diaphoresis, or absence of any symptoms) are also possible, especially in women, the elderly, and those with diabetes.
- Stable angina is promptly relieved by rest or *nitroglycerin*, whereas unstable angina occurs with increased frequency, duration, and intensity and is not relieved by rest or *nitroglycerin.* Unstable angina is an acute coronary syndrome requiring acute medical attention to prevent progression to MI and death.
- β-Blockers, calcium channel blockers, organic nitrates, and the sodium channel–blocking drug *ranolazine* are used either alone or in combination to manage stable angina.
- β-Blockers decrease myocardial oxygen demand by decreasing heart rate and contractility. β-Blockers are recommended as initial antianginal therapy unless contraindicated (except for vasospastic angina where β-blockers can worsen symptoms). Cardioselective β1-blockers are preferred; β-blockers with intrinsic sympathomimetic activity should be avoided.
- Calcium channel blockers are arterial vasodilators (especially dihydropyridines). Calcium channel blockers are preferred for treatment of vasospastic angina. Nondihydropyridine calcium channel blockers also have negative inotropic effects and should be avoided in patients with heart failure with reduced ejection fraction.
- Nitrates reduce preload and dilate coronary arteries. All patients should have *nitroglycerin* on hand to treat acute angina attacks. A nitrate-free interval on longer-acting nitrates and transdermal formulations is required to prevent tolerance.
- The sodium channel–blocking drug *ranolazine* is typically used in patients who have failed other therapies for stable angina. It can prolong the QT

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interval and is subject to numerous drug interactions. It is less effective in women.

STUDY QUESTIONS

Choose the ONE best answer.

12.1 Which of the following medications should be prescribed to all angina patients to treat an acute attack?

A. Isosorbide mononitrate
B. Propranolol
C. Nitroglycerin sublingual tablet or spray
D. Ranolazine

Correct answer = C. The other options will not provide prompt relief of angina and should not be used to treat an acute attack.

12.2 Which of the following instructions is important to communicate to a patient receiving a prescription for the nitroglycerin patch?

A. Apply the patch at onset of angina symptoms for quick relief.
B. Remove the old patch after 24 hours of use, then immediately apply the next patch to prevent any breakthrough angina pain.
C. Do not use sublingual nitroglycerin in combination with the patch.
D. Ensure a nitrate-free interval of 10 to 12 hours every day to prevent development of nitrate tolerance.

Correct answer = D. Nitrate-free intervals help prevent the development of nitrate tolerance. Sublingual nitroglycerin should be used to treat breakthrough angina due to its quick onset of action; transdermal nitroglycerin has a delayed onset of action.

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12.3 Which of the following correctly ranks the calcium channel blockers from most peripherally active to most active centrally on the myocardium?

A. Diltiazem, amlodipine, verapamil
B. Verapamil, diltiazem, nifedipine
C. Nifedipine, verapamil, diltiazem
D. Amlodipine, diltiazem, verapamil

Correct answer = D. Amlodipine (like nifedipine) is a peripheral vasodilator, diltiazem is intermediate with actions on both myocardial and peripheral calcium channels, and verapamil has the most negative inotropic effects.

12.4 A 74-year-old man with a recent MI is experiencing typical angina pain that is relieved with rest and sublingual nitroglycerin. His blood pressure is well controlled (126/73 mm Hg), and his heart rate is 81 bpm. Which is the most appropriate therapy for his angina?

A. Nitroglycerin patch
B. Verapamil
C. Metoprolol
D. Felodipine

Correct answer = C. β-Blockers reduce the risk of death and MI in patients who have had a prior MI, making metoprolol the best answer. The other answers would be reasonable as add-on therapy if he remains symptomatic after titration of metoprolol or if he is unable to tolerate a β-blocker.

12.5 A 68-year-old woman experiences chest pain that requires her to take frequent rest breaks while shopping at the grocery store. She is adherent to a maximized dose of β-blocker. Her resting heart rate is low (54) and blood pressure in clinic today is elevated (154/82 mm Hg). She has been unable to tolerate an increase in isosorbide mononitrate due to headache. Which

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of the following is the most appropriate addition to her antianginal therapy?

A. Amlodipine
B. Diltiazem
C. Ranolazine
D. Verapamil

Correct answer = A. Amlodipine is the best answer as it will also help control her hypertension. The patient's heart rate is relatively low; diltiazem and verapamil could decrease the heart rate further. Ranolazine can be used when other agents are maximized but is less effective in women and would not help to lower her blood pressure.

12.6 Which of the following is correct regarding antianginal therapy in patients with heart failure with reduced ejection fraction?

A. β-Blockers have been associated with reduced mortality.
B. Dihydropyridine calcium channel blockers should be avoided.
C. β-Blockers with ISA are preferred over those without ISA.
D. Nondihydropyridine calcium channel blockers should be used in patients with heart failure with reduced ejection fraction who cannot tolerate β-blockers.

Correct answer = A. β-Blockers have been shown to reduce mortality in heart failure with reduced ejection fraction, but β-blockers with ISA should be avoided in these patients. Dihydropyridine calcium channel blockers can be used in patients with heart failure with reduced ejection fraction, but nondihydropyridine calcium channel blockers should be avoided due to negative inotropic effects.

12.7 A 45-year-old woman with type 1 diabetes has been diagnosed with Prinzmetal angina. Which of the following is correct regarding management of angina in this patient?

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A. β-Blockers are the treatment of choice but should be avoided because of her diabetes.
B. Nitroglycerin is not beneficial for this type of angina.
C. She should be counseled to take nitroglycerin before physical activity to prevent symptoms.
D. Felodipine will be more effective than verapamil.

Correct answer = D. Prinzmetal or vasospastic angina responds well to vasodilators, including the dihydropyridine calcium channel blocker felodipine. Verapamil is a weak vasodilator. β-Blockers may be used with caution in patients with diabetes, but these drugs are less effective options for Prinzmetal angina. Nitrates are also effective, but Prinzmetal angina is provoked by coronary artery vasospasm rather than physical activity.

12.8 A 56-year-old man with stable angina is being evaluated in the emergency department for an asthma exacerbation. Which of his home medications may impact the effectiveness of bronchodilator therapy?

A. Amlodipine
B. Propranolol
C. Nitroglycerin spray
D. Valsartan

Correct answer = B. Nonselective β-blockers should be avoided in patients with asthma as they may block the effects of β-agonist bronchodilators used for rescue therapy. The other medications will not affect bronchodilator effectiveness.

12.9 An 83-year-old man with diabetes on basal-bolus insulin therapy is being prescribed a β-blocker for his angina. Which of the following is correct for this patient?

A. An alternative should be prescribed because β-blockers are contraindicated in patients with diabetes.
B. He will need to reduce his insulin dose because β-blockers can cause hypoglycemia.

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C. He may experience symptoms of hypoglycemia even with normal blood glucose levels due to the effect of the β-blocker on adrenergic receptors.
D. β-Blockers can blunt hypoglycemia awareness.- Diaphoresis may become his primary alert symptom of hypoglycemia.

Correct answer = D. β-Blockers can be used in patients with diabetes but patients need to be counseled that they may be at higher risk for hypoglycemia unawareness. β-Blockers can block norepinephrine's effects on adrenergic receptors, which can leave diaphoresis as the primary autonomic symptom in these patients.

12.10 Which of the following can be safely used with ranolazine?

A. Carbamazepine
B. Quetiapine
C. Warfarin
D. Fluconazole

Correct answer = C. Carbamazepine is a CYP 3A4 inducer, and fluconazole is a CYP 3A4 inhibitor and would have significant effects on ranolazine drug levels. Quetiapine, like ranolazine, can cause QT prolongation; therefore, the combination should be avoided.

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13

Anticoagulants and Antiplatelet Agents

Katherine Vogel Anderson, Kimberly Atkinson

I. OVERVIEW

This chapter describes drugs that are useful in the treatment of disorders of hemostasis. Thrombosis, the formation of an unwanted clot within a blood vessel, is the most common abnormality of hemostasis. Thrombotic disorders include acute myocardial infarction (MI), deep vein thrombosis (DVT), pulmonary embolism (PE), and acute ischemic stroke. These conditions are treated with drugs such as anticoagulants and fibrinolytics. Bleeding disorders related to the failure of hemostasis are less common than thromboembolic disorders. Bleeding disorders include hemophilia, which is treated with transfusion of recombinant factor VIII, and vitamin K deficiency, which is treated with vitamin K supplementation. Figure 13.1 summarizes agents used for the treatment of dysfunctions of hemostasis.

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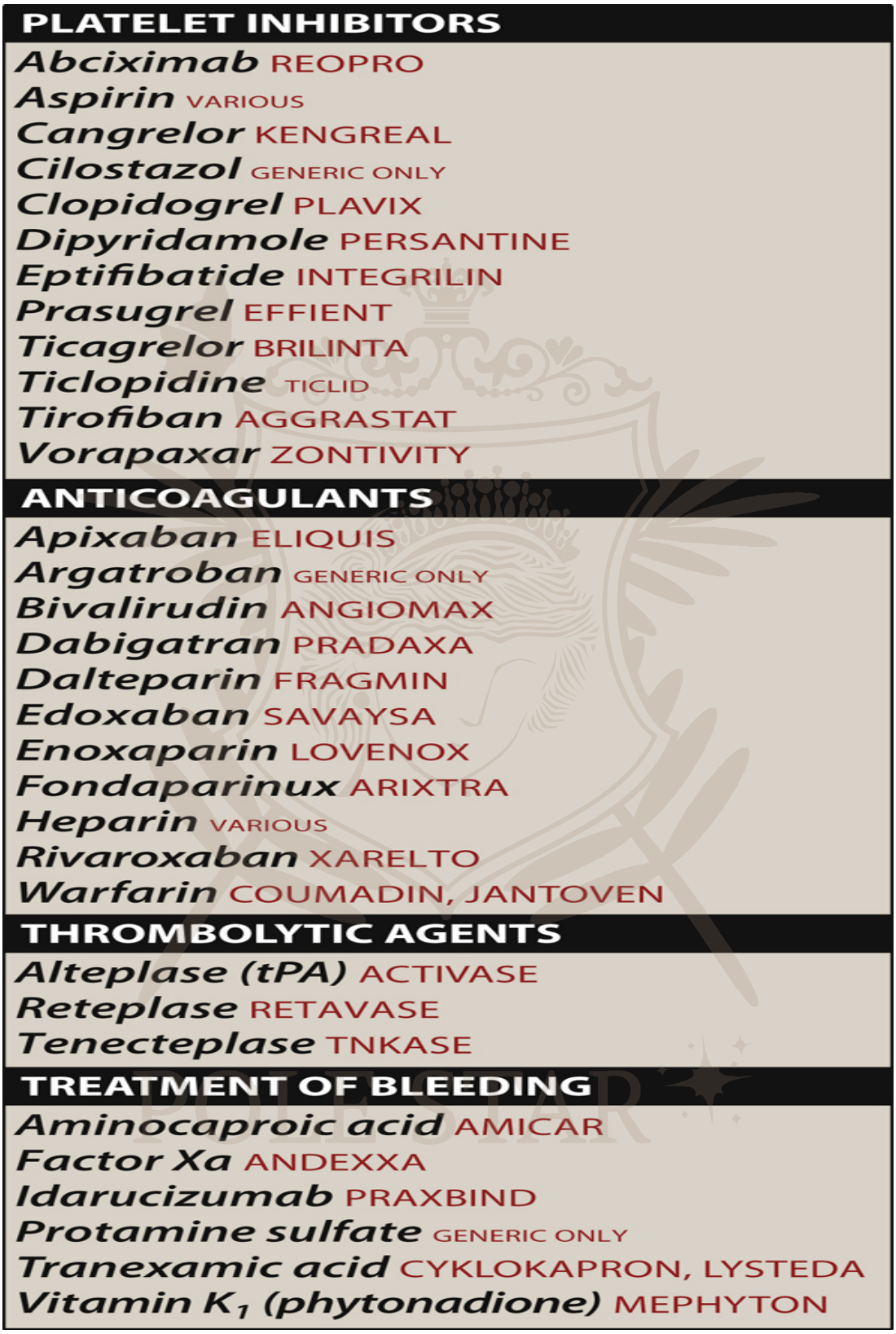

Figure 13.1 Summary of drugs used in treating dysfunctions of hemostasis.

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II. THROMBUS VERSUS EMBOLUS

A clot that adheres to a vessel wall is called a “thrombus,” whereas an intravascular clot that floats in the blood is termed an “embolus.” Thus, a detached thrombus becomes an embolus. Both thrombi and emboli are dangerous, because they may occlude blood vessels and deprive tissues of oxygen and nutrients. Arterial thrombosis most often occurs in medium-sized vessels rendered thrombogenic by atherosclerosis. Arterial thrombosis usually consists of a platelet-rich clot. In contrast, venous thrombosis is triggered by blood stasis or inappropriate activation of the coagulation cascade. Venous thrombosis typically involves a clot that is rich in fibrin, with fewer platelets than are observed with arterial clots.

III. PLATELET RESPONSE TO VASCULAR INJURY

Physical trauma to the vascular system, such as a puncture or a cut, initiates a complex series of interactions between platelets, endothelial cells, and the coagulation cascade. These interactions lead to hemostasis or the cessation of blood loss from a damaged blood vessel. Platelets are central in this process. Initially, there is vasospasm of the damaged blood vessel to prevent further blood loss. The next step involves the formation of a platelet–fibrin plug at the site of the puncture. The creation of an unwanted thrombus involves many of the same steps as normal clot formation, except that the triggering stimulus is a pathologic condition in the vascular system, rather than external physical trauma.

A. Resting platelets

Platelets act as vascular sentries, monitoring the integrity of the vascular endothelium. In the absence of injury, resting platelets circulate freely, because the balance of chemical signals indicates that the vascular system is not damaged (Figure 13.2, [1]).

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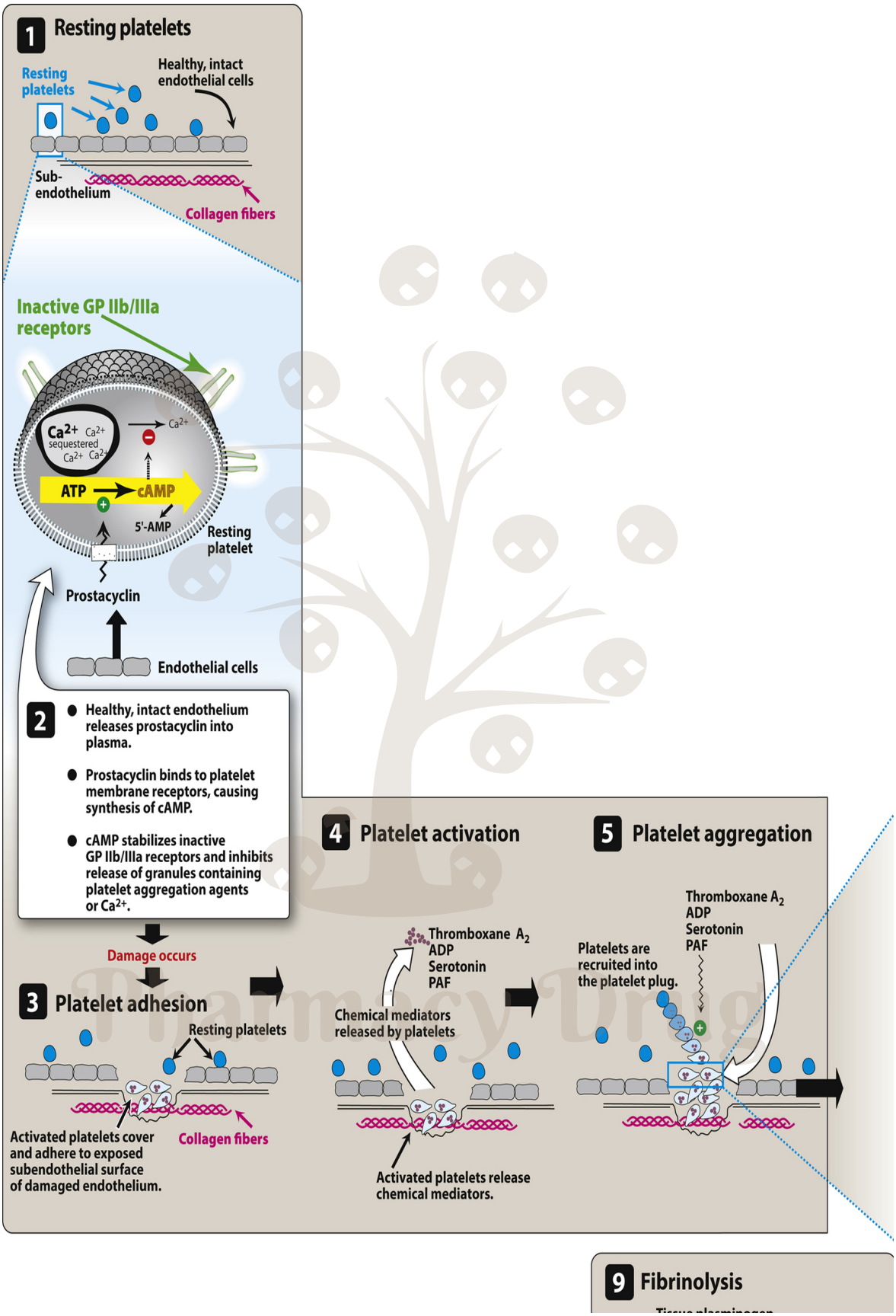

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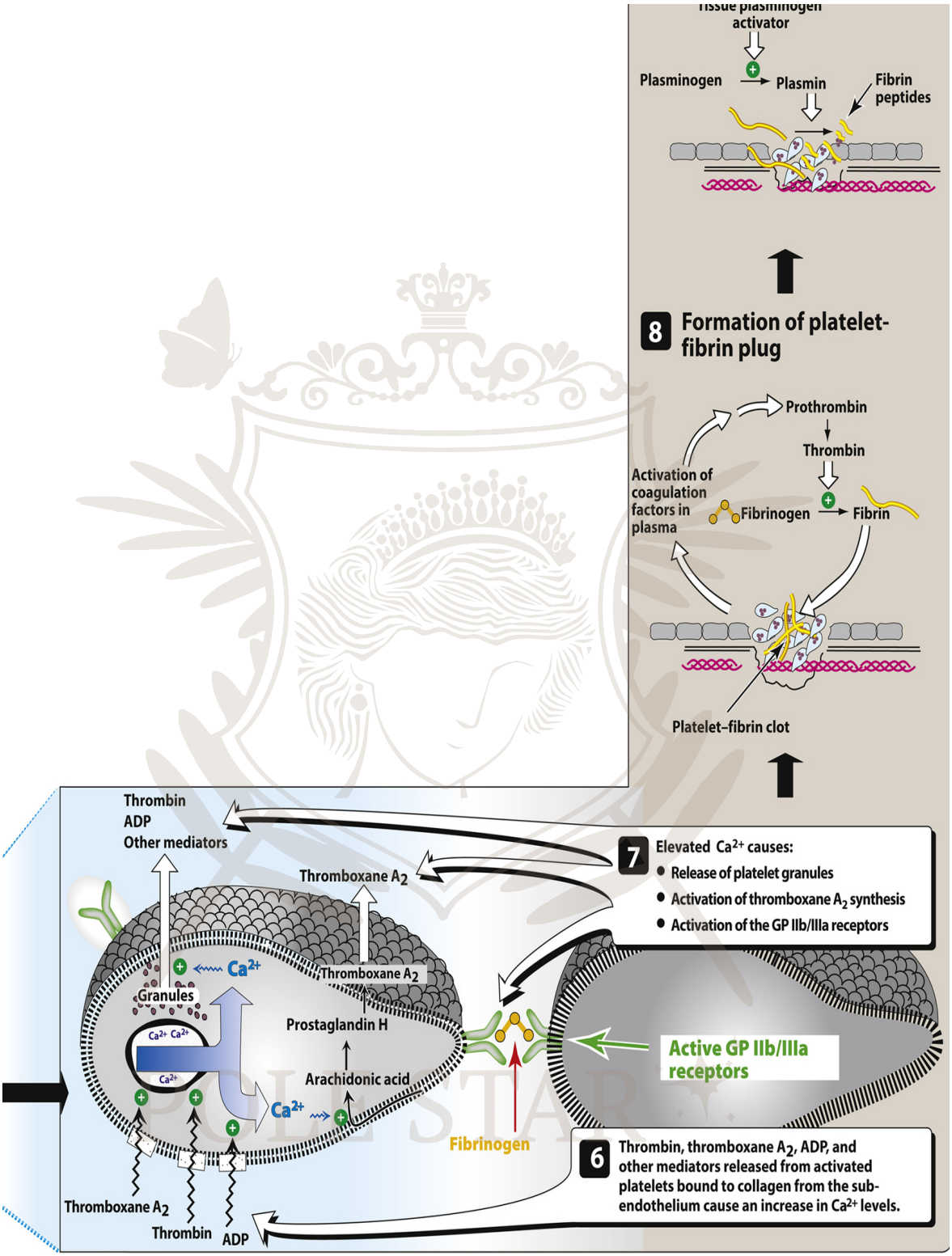

Figure 13.2 Formation of a hemostatic plug.ADP = adenosine diphosphate; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; GP = glycoprotein; PAF = platelet activation factor.

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1.Chemical mediators synthesized by endothelial cells: Prostacyclin is synthesized by intact endothelial cells and acts as an inhibitor of platelet aggregation. Prostacyclin (also known as prostaglandin I_2) binds to platelet membrane receptors that are coupled to the synthesis of cyclic adenosine monophosphate (cAMP), an intracellular messenger (Figure 13.2, [2]). Elevated levels of intracellular cAMP are associated with a decrease in intracellular calcium. Decreased intracellular calcium prevents platelet activation and the subsequent release of platelet aggregation agents. Damaged endothelial cells synthesize less prostacyclin than healthy cells. With less prostacyclin to bind platelet receptors, less intracellular cAMP is synthesized; this leads to platelet aggregation.

2.Roles of thrombin, thromboxanes, and collagen: The platelet membrane also contains receptors that can bind thrombin, thromboxanes, and exposed collagen. In the intact, normal vessel, circulating levels of thrombin and thromboxane are low, and the intact endothelium covers collagen in the subendothelial layers. The corresponding platelet receptors are, thus, unoccupied, and as a result, platelet activation and aggregation are not initiated. However, when occupied, each of these receptor types triggers a series of reactions leading to the release into the circulation of intracellular granules by the platelets. This ultimately stimulates platelet aggregation.

B. Platelet adhesion

When the endothelium is injured, platelets adhere to and virtually cover the exposed collagen of the subendothelium (Figure 13.2, [3]). This triggers a complex series of chemical reactions, resulting in platelet activation.

C. Platelet activation

Receptors on the surface of the adhering platelets are activated by the collagen of the underlying connective tissue. This causes morphologic changes in platelets (Figure 13.3) and the release of platelet granules containing chemical mediators, such as adenosine diphosphate

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(ADP), thromboxane A_2, serotonin, platelet activation factor, and thrombin (Figure 13.2, [4]). These signaling molecules bind to receptors in the outer membrane of resting platelets circulating nearby. These receptors function as sensors that are activated by the signals sent from the adhering platelets. The previously dormant platelets become activated and start to aggregate. These actions are mediated by several messenger systems that ultimately result in elevated levels of calcium and a decreased concentration of cAMP within the platelet.

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Figure 13.3 Scanning electron micrograph of platelets.

D. Platelet aggregation

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The increase in cytosolic calcium accompanying activation is due to a release of sequestered stores within the platelet (Figure 13.2, [5,6,7]). This leads to (1) the release of platelet granules containing mediators, such as ADP and serotonin, that activate other platelets; (2) activation of thromboxane A_2 synthesis; and (3) activation of glycoprotein (GP) IIb/IIIa receptors that bind fibrinogen and, ultimately, regulate platelet–platelet interaction and thrombus formation. Fibrinogen, a soluble plasma GP, simultaneously binds to GP IIb/IIIa receptors on two separate platelets, resulting in platelet cross-linking and platelet aggregation. This leads to an avalanche of platelet aggregation, because each activated platelet can recruit other platelets (Figure 13.4).

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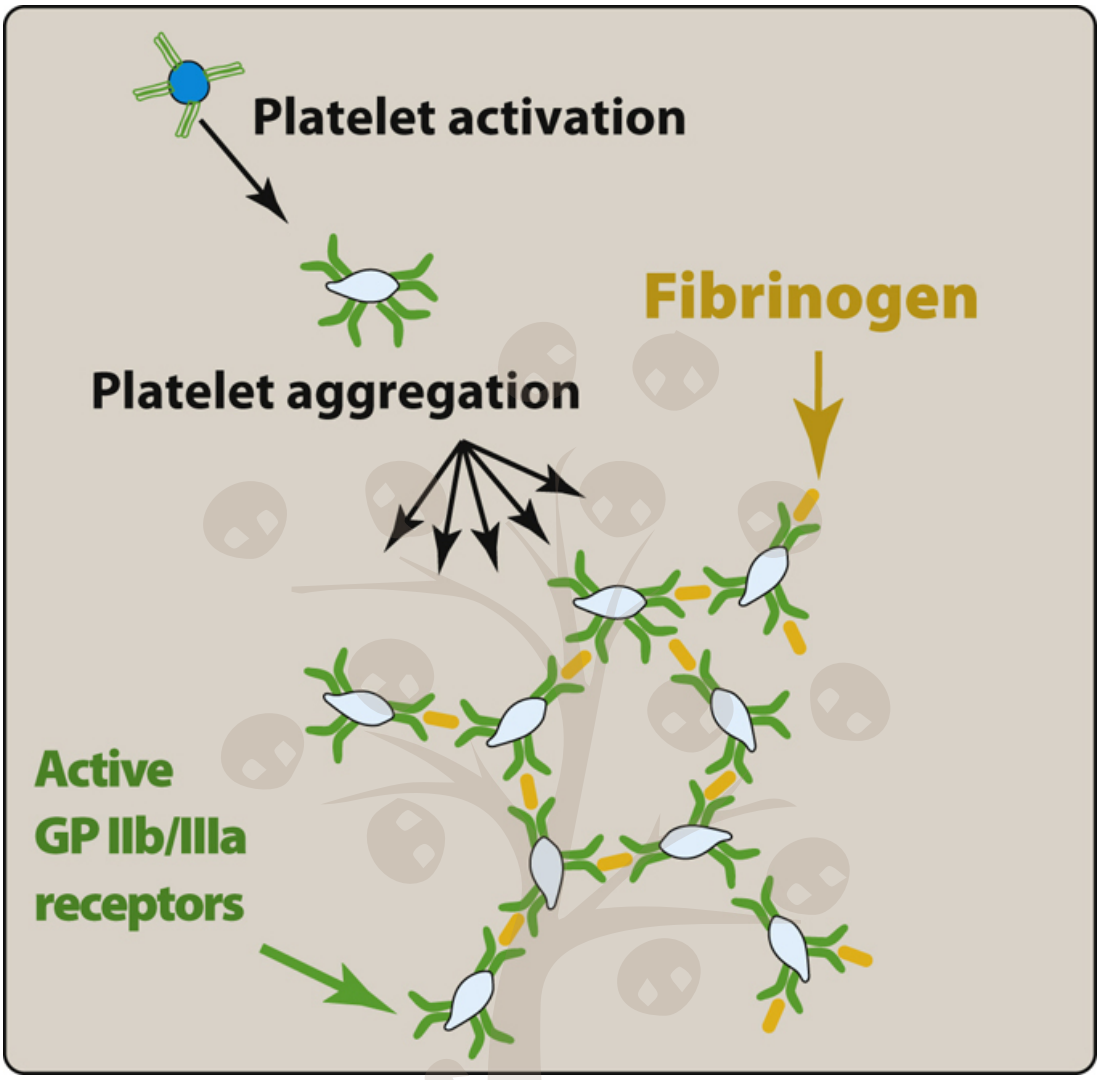

Figure 13.4 Activation and aggregation of platelets.GP = glycoprotein.

E. Formation of a clot

Local stimulation of the coagulation cascade by tissue factors released from the injured tissue and by mediators on the surface of platelets results in the formation of thrombin (factor IIa). In turn, thrombin, a serine protease, catalyzes the hydrolysis of fibrinogen to fibrin, which is incorporated into the clot. Subsequent cross-linking of the fibrin strands stabilizes the clot and forms a hemostatic platelet–fibrin plug (Figure 13.2, [8]).

F. Fibrinolysis

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During clot formation, the fibrinolytic pathway is locally activated. Plasminogen is enzymatically processed to plasmin (fibrinolysin) by plasminogen activators in the tissue (Figure 13.2, [9]). Plasmin limits the growth of the clot and dissolves the fibrin network as wounds heal.

IV. PLATELET AGGREGATION INHIBITORS

Platelet aggregation inhibitors decrease the formation of a platelet-rich clot or decrease the action of chemical signals that promote platelet aggregation (Figure 13.5). The platelet aggregation inhibitors described below inhibit cyclooxygenase-1 (COX-1), block GP IIb/IIIa, or block ADP receptors, thereby interfering with the signals that promote platelet aggregation. These agents are beneficial in the prevention and treatment of occlusive cardiovascular diseases, in the maintenance of vascular grafts and arterial patency, and as adjuncts to thrombin inhibitors or thrombolytic therapy in MI.

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Medication	Adverse Effects	Drug Interactions	Monitoring Parameters
Oral Agents:			
Aspirin	Angioedema Bleeding Bronchospasm GI disturbances Reye syndrome SJS	Anticoagulants, P2Y12 inhibitors, NSAIDs—increased bleeding *cidofovir*—nephrotoxicity *methotrexate*—increased toxicity *probenecid*—decreased uricosuric effects	CBC LFT
Cilostazol	Bleeding GI disturbances Headache Peripheral edema SJS	Food (administer on empty stomach)	CBC
Clopidogrel	Bleeding SJS	Strong CYP2C19 inhibitors reduce antiplatelet effect (e.g., *omeprazole*)	CBC LFT
Dipyridamole	Bleeding Dizziness GI discomfort Rash	Salicylates—increased bleeding Thrombolytic agents—increased bleeding	None
Prasugrel	Angioedema Bleeding Headache Hyperlipidemia Hypertension	Anticoagulants—increased bleeding Other antiplatelets—increased bleeding	CBC
Ticagrelor	Bleeding Dyspnea Headache Raised SCr	Strong CYP3A4 inhibitors (e.g., *ketoconazole*)—increased bleeding Strong CYP3A4 inducers (e.g., *rifampin*)—decreased efficacy	CBC LFT
Injectable Agents:			
Abciximab *Eptifibatide* *Tirofiban*	For all agents: Hypotension Nausea Vomiting Thrombocytopenia	For all agents: Increased bleeding: *Ginkgo biloba* Antiplatelets Salicylates SSRIs and SNRIs	For all agents: APTT clotting time H/H platelet count thrombin time

Figure 13.5 Summary of characteristics of platelet aggregation inhibitors.APTT = activated partial thromboplastin time, CBC = complete blood count, GI = gastrointestinal, H/H = hemoglobin and hematocrit, LFT = liver function test, NSAID = nonsteroidal anti-inflammatory drug, SCr = serum creatinine, SJS = Stevens–Johnson syndrome, SNRI = serotonin–norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

A. Aspirin

1.Mechanism of action: Stimulation of platelets by thrombin, collagen, and ADP results in activation of platelet membrane phospholipases that liberate arachidonic acid from membrane phospholipids. Arachidonic acid is first converted to prostaglandin H_2 by COX-1 (Figure 13.6). Prostaglandin H_2 is further metabolized to thromboxane A_2, which is released into plasma. Thromboxane A_2 promotes the aggregation process that is essential for the rapid formation of a hemostatic plug. *Aspirin* [AS-pir-in] inhibits

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thromboxane A_2 synthesis by acetylation of a serine residue on the active site of COX-1, thereby irreversibly inactivating the enzyme (Figure 13.7). This shifts the balance of chemical mediators to favor the antiaggregatory effects of prostacyclin, thereby preventing platelet aggregation. The inhibitory effect is rapid, and *aspirin*-induced suppression of thromboxane A_2 and the resulting suppression of platelet aggregation last for the life of the platelet, which is approximately 7 to 10 days. Repeated administration of *aspirin* has a cumulative effect on the function of platelets. *Aspirin* is the only antiplatelet agent that irreversibly inhibits platelet function.

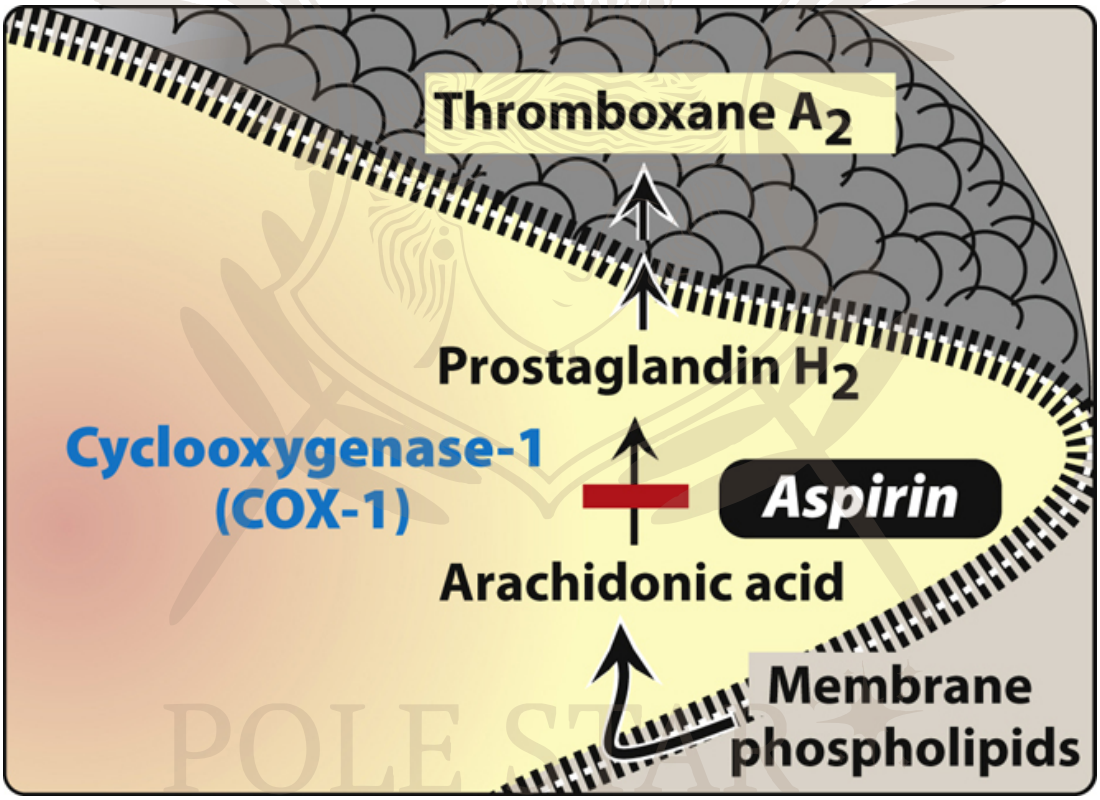

Figure 13.6 *Aspirin* irreversibly inhibits platelet cyclooxygenase-1.

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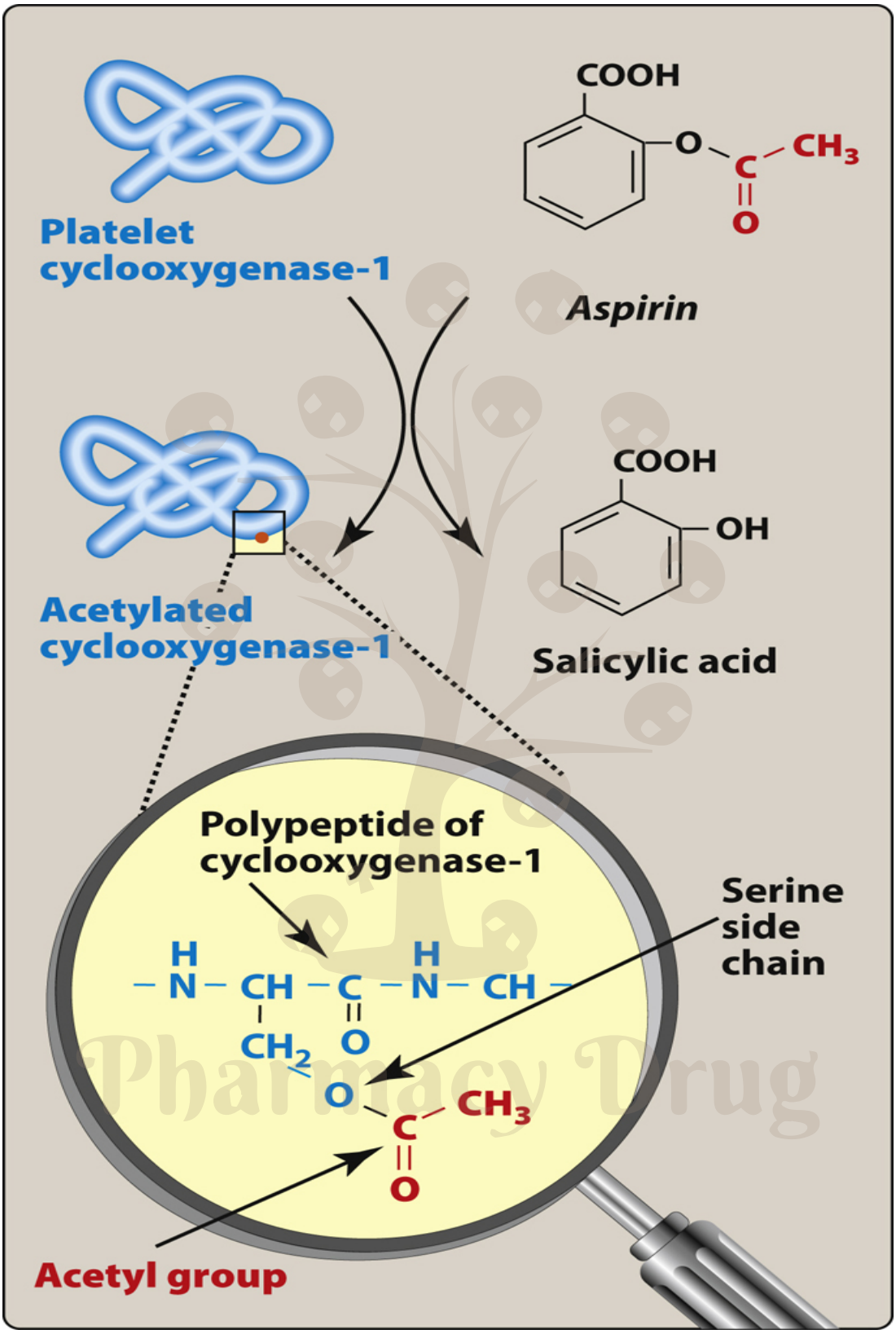

Figure 13.7 Acetylation of cyclooxygenase-1 by *aspirin*.

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2.Therapeutic use: *Aspirin* is used in the prophylactic treatment of transient cerebral ischemia, to reduce the incidence of recurrent MI and to decrease mortality in the setting of primary and secondary prevention of MI. Complete inactivation of platelets occurs with 75 mg of *aspirin* given daily. The recommended antiplatelet dose of *aspirin* ranges from 50 to 325 mg daily. [Note: *Aspirin* is also used for treatment of inflammation, pain, and fever (see Chapter 40).]

3.Pharmacokinetics: When given orally, *aspirin* is absorbed by passive diffusion and quickly hydrolyzed to salicylic acid in the liver. Salicylic acid is further metabolized in the liver, and some is excreted unchanged in the urine. The half-life of *aspirin* ranges from 15 to 20 minutes, and for salicylic acid it is 3 to 12 hours.

4.Adverse effects: Higher doses of *aspirin* increase drug-related toxicities as well as the probability that *aspirin* may also inhibit prostacyclin production. Bleeding time is prolonged by *aspirin* treatment, causing complications that include an increased incidence of hemorrhagic stroke and gastrointestinal (GI) bleeding, especially at higher doses of the drug. Nonsteroidal anti-inflammatory drugs, such as *ibuprofen*, inhibit COX-1 by transiently competing at the catalytic site (see Chapter 40). *Ibuprofen*, if taken within the 2 hours prior to *aspirin*, can obstruct the access of *aspirin* to the serine residue and, thereby, antagonize platelet inhibition by *aspirin.* Therefore, immediate-release *aspirin* should be taken at least 60 minutes before or at least 8 hours after *ibuprofen*.

B. $P2Y_{12}$ receptor antagonists

Ticlopidine [ti-KLOE-pi-deen], *clopidogrel* [kloh-PID-oh-grel], *prasugrel* [PRA-soo-grel], *ticagrelor* [tye-KA-grel-or], and *cangrelor* [KAN-grel-or] are $P2Y_{12}$ ADP receptor inhibitors that also block platelet aggregation but by a mechanism different from that of *aspirin.* All of these agents are administered orally, with the exception of *cangrelor*, which is an injectable formulation.

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1.Mechanism of action: These drugs inhibit the binding of ADP to the $P2Y_{12}$ receptor on platelets and, thereby, inhibit the activation of the GP IIb/IIIa receptors required for platelets to bind to fibrinogen and to each other (Figure 13.8). *Ticagrelor* and *cangrelor* bind to the $P2Y_{12}$ ADP receptor in a reversible manner. The other agents bind irreversibly. The maximum inhibition of platelet aggregation is achieved in 2 minutes with intravenous (IV) *cangrelor*, 1 to 3 hours with *ticagrelor*, 2 to 4 hours with *prasugrel*, 3 to 4 days with *ticlopidine*, and 3 to 5 days with *clopidogrel.* When treatment is suspended, the platelet system requires time to recover.

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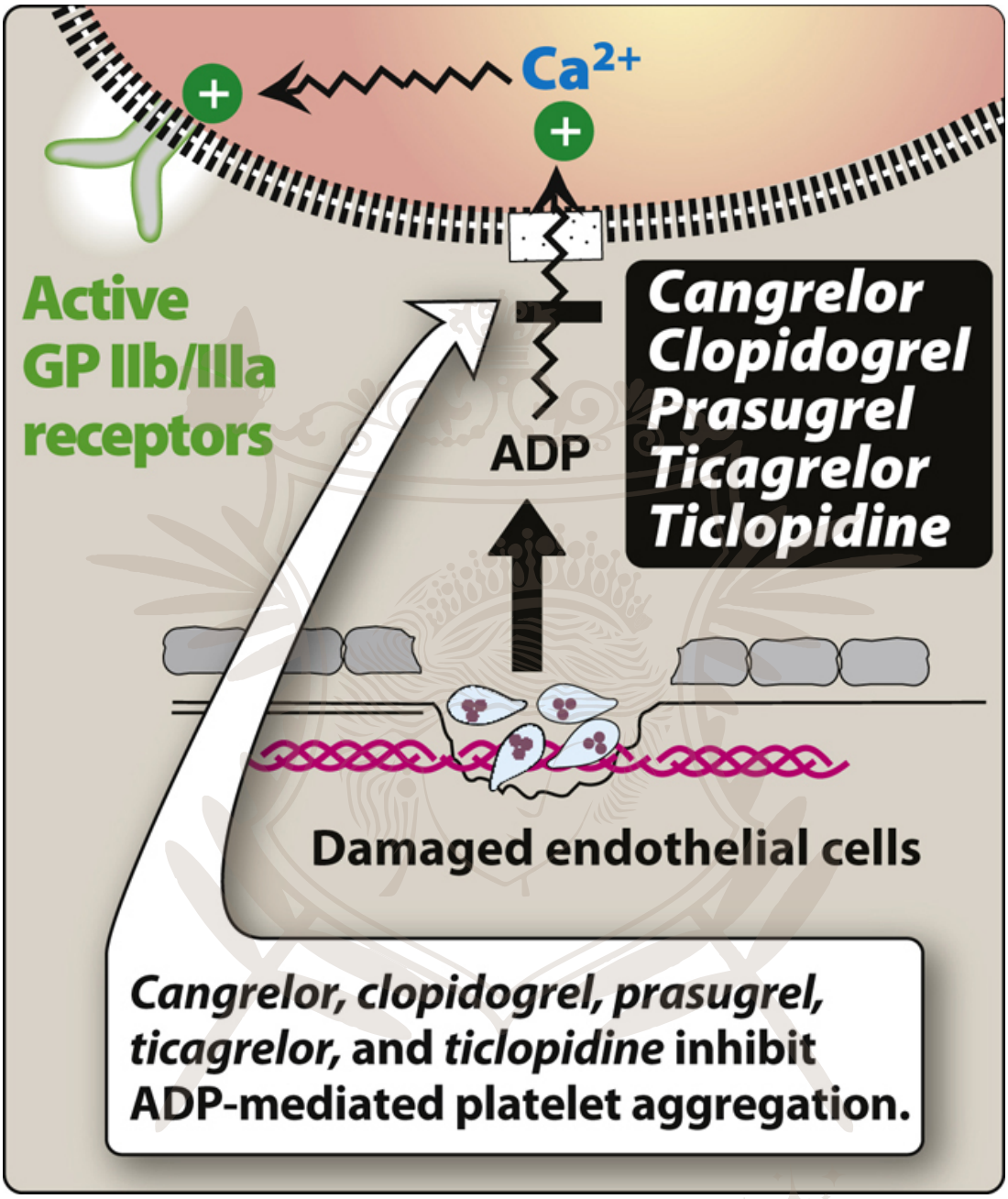

Figure 13.8 Mechanism of action of $P2Y_{12}$ receptor antagonists.ADP = adenine diphosphate; GP = glycoprotein.

2.Therapeutic use: *Clopidogrel* is approved for prevention of atherosclerotic events in patients with a recent MI or stroke and in those with established peripheral arterial disease. It is also approved for prophylaxis of thrombotic events in acute coronary

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syndromes (unstable angina or non–ST-elevation MI). Additionally, *clopidogrel* is used to prevent thrombotic events associated with percutaneous coronary intervention (PCI) with or without coronary stenting. *Ticlopidine* is similar in structure to *clopidogrel.* It is indicated for the prevention of transient ischemic attacks (TIA) and strokes in patients with a prior cerebral thrombotic event. However, due to life-threatening hematologic adverse reactions, *ticlopidine* is generally reserved for patients who are intolerant or allergic to *aspirin* therapy. *Prasugrel* is approved to decrease thrombotic cardiovascular events in patients with acute coronary syndromes (unstable angina, non–ST-elevation MI, and ST-elevation MI managed with PCI). *Ticagrelor* is approved for the prevention of arterial thromboembolism in patients with unstable angina and acute MI, including those undergoing PCI. *Cangrelor* is approved as an adjunct during PCI to reduce thrombotic events in select patients.

3.Pharmacokinetics: These agents require oral loading doses for quicker antiplatelet effect, except *cangrelor* that has a fast onset of action with intravenous administration. Food interferes with the absorption of *ticlopidine* but not with the other agents. After oral ingestion, the drugs are extensively bound to plasma proteins. They undergo hepatic metabolism by the cytochrome P-450 (CYP) system to active metabolites. Elimination of the drugs and metabolites occurs by both the renal and fecal routes. *Clopidogrel* is a prodrug, and its therapeutic efficacy relies on its active metabolite, which is produced via metabolism by CYP 2C19. Genetic polymorphism of CYP 2C19 leads to a reduced clinical response in patients who are “poor metabolizers” of *clopidogrel*. Tests are currently available to identify poor metabolizers, and it is recommended that other antiplatelet agents (*prasugrel* or *ticagrelor*) be prescribed for these patients. In addition, other drugs that inhibit CYP 2C19, such as *omeprazole* and *esomeprazole*, should be avoided while on *clopidogrel*.

4.Adverse effects: These agents can cause prolonged bleeding for which there is no antidote. *Ticlopidine* is associated with severe hematologic reactions that limit its use, such as agranulocytosis, thrombotic thrombocytopenic purpura (TTP), and

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aplastic anemia. *Clopidogrel* causes fewer adverse reactions, and the incidence of neutropenia is lower. While all of the $P2Y_{12}$ inhibitors have a risk of TTP, it is considered rare. *Prasugrel* is contraindicated in patients with history of TIA or stroke. *Prasugrel*, *ticagrelor*, and *cangrelor* carry boxed warnings for bleeding. Additionally, *ticagrelor* carries a boxed warning for diminished effectiveness with concomitant use of *aspirin* doses above 100 mg.

Clinical Application 13.1: Transitioning Between $P2Y_{12}$ Inhibitors

Because of intolerance or a change in prescription coverage, patients may need to switch $P2Y_{12}$ inhibitors. As such, it is important to know if the patient is in the acute phase (30 days or less) or late phase (31 days or longer) following the cardiovascular event for which they are prescribed the $P2Y_{12}$ inhibitor. Patients in the acute phase need to take a loading dose of the new $P2Y_{12}$ inhibitor 24 hours after stopping the previous agent. This is to ensure that platelet inhibition is maximized. For example, when switching from *ticagrelor* to *prasugrel*, a patient should take a loading dose of *prasugrel* 24 hours after stopping *ticagrelor*, and then proceed with *prasugrel* once daily as normal. If patients are in the late phase, then loading doses are not necessary except when changing from *ticagrelor* to *clopidogrel* or *prasugrel.* In this case, loading doses of *clopidogrel* or *prasugrel* are recommended because of the rapid offset of action of *ticagrelor*.

C. Glycoprotein IIb/IIIa inhibitors

1.Mechanism of action: The GP IIb/IIIa receptor plays a key role in stimulating platelet aggregation (Figure 13.9). *Eptifibatide* [ep-ti-FIB-ih-tide] and *tirofiban* [tye-roe-FYE-ban] block the GP IIb/IIIa receptor. *Eptifibatide* is a cyclic peptide that binds to GP IIb/IIIa at the site that interacts with the arginine–glycine–aspartic acid sequence of fibrinogen. *Tirofiban* is not a peptide, but it blocks the same site as *eptifibatide.* [Note: *Abciximab* [ab-SIKS-eh-mab] is also a GP IIb/IIIa inhibitor, although it is not available in the United States.]

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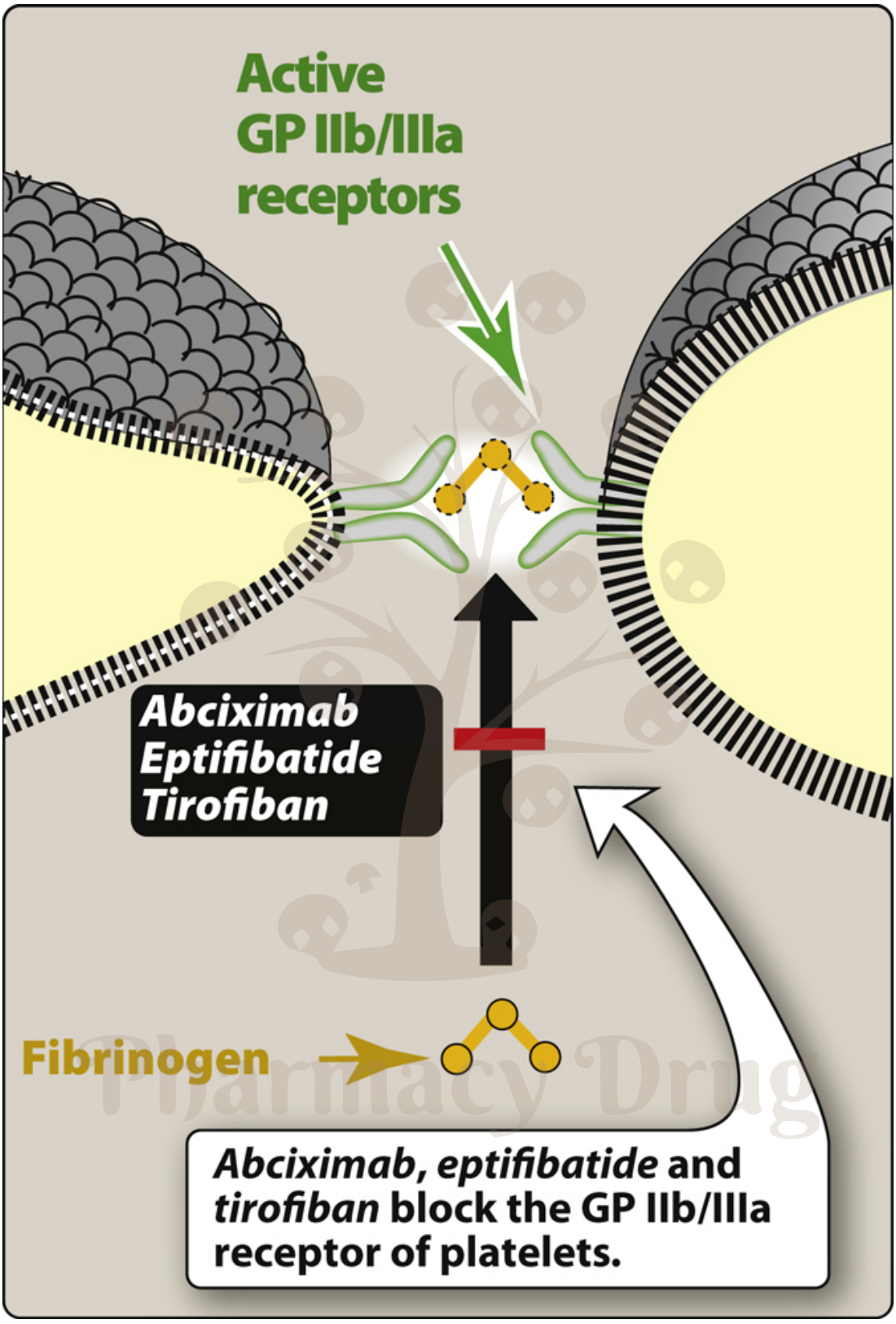

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Figure 13.9 Mechanism of action of glycoprotein (GP) IIb/IIIa receptor blockers.Data from D. J.Schneider , P. B.Tracy , and B. E.Sobel . *Hosp. Pract*. 107 (1998).

2.Therapeutic use: These agents are given intravenously, along with *heparin* and *aspirin*, as an adjunct to PCI for the prevention of cardiac ischemic complications. Overall, use of these agents has decreased due to the approval of newer antiplatelet agents.

3.Pharmacokinetics: *Eptifibatide* and *tirofiban* are given by IV infusion. When the IV infusion of *eptifibatide* or *tirofiban* is stopped, both agents are rapidly cleared from the plasma. *Eptifibatide* and its metabolites are excreted by the kidney. *Tirofiban* is excreted largely unchanged by the kidney and to a lesser extent in the feces.

4.Adverse effects: The major adverse effect of these agents is bleeding, especially if used with anticoagulants.

D. Dipyridamole

Dipyridamole [dye-peer-ID-a-mole], a coronary vasodilator, increases intracellular levels of cAMP by inhibiting phosphodiesterase, thereby resulting in decreased thromboxane A_2 synthesis. The drug may potentiate the effect of prostacyclin and, therefore, decrease platelet adhesion to thrombogenic surfaces (Figure 13.2). *Dipyridamole* is used for stroke prevention and is given in combination with another antiplatelet agent such as *aspirin,* since it has weak antiplatelet effects on its own. *Dipyridamole* has variable bioavailability following oral administration. It is highly protein bound. The drug undergoes hepatic metabolism, mainly glucuronidation, and is excreted primarily in the feces. Patients with unstable angina should not use *dipyridamole* because of its vasodilating properties, which may worsen ischemia (coronary steal phenomenon). *Dipyridamole* commonly causes headache and dizziness and can lead to orthostatic hypotension (especially if administered IV).

E. Cilostazol

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Cilostazol [sill-AH-sta-zole] is an oral antiplatelet agent that also has vasodilating activity. *Cilostazol* and its active metabolites inhibit phosphodiesterase type III, which prevents the degradation of cAMP, thereby increasing levels of cAMP in platelets and vascular tissues. The increase in cAMP prevents platelet aggregation and promotes vasodilation of blood vessels, respectively. *Cilostazol* is approved to reduce the symptoms of intermittent claudication. *Cilostazol* is extensively metabolized in the liver by the CYP 3A4 and 2C19 isoenzymes. As such, this agent has many drug interactions that require dose modification. The primary route of elimination is via the kidney. Headache and GI side effects (diarrhea, abnormal stools, dyspepsia, and abdominal pain) are the most common adverse effects with *cilostazol.* Rarely, thrombocytopenia or leukopenia has been reported. Phosphodiesterase type III inhibitors have been shown to increase mortality in patients with advanced heart failure. As such, *cilostazol* is contraindicated in patients with heart failure.

F. Vorapaxar

Vorapaxar is an antagonist of the protease-activated receptor-1 (a thrombin receptor) expressed on platelets. Although it binds reversibly, it has a long half-life and an extended duration of action in which the effects may be seen up to 4 weeks after discontinuation. It is an oral drug that is indicated in conjunction with *aspirin* or *clopidogrel* to reduce cardiovascular events in patients with a history of MI or with peripheral artery disease. It should not be given to patients with a high risk of bleeding, including patients with a history of stroke, transient ischemic attack, or intracranial hemorrhage.

V. BLOOD COAGULATION

The coagulation process that generates thrombin consists of two interrelated pathways, the extrinsic and the intrinsic systems (Figure 13.10). The extrinsic system is initiated by the activation of clotting factor VII by tissue factor (also known as thromboplastin). Tissue factor is a membrane protein that is normally separated from the blood by the endothelial cells that line the vasculature. However, in response to vascular injury, tissue factor becomes exposed to blood. There, it can

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bind and activate factor VII, initiating the extrinsic pathway. The intrinsic system is triggered by the activation of clotting factor XII. This occurs when blood comes into contact with the collagen in the damaged wall of a blood vessel.

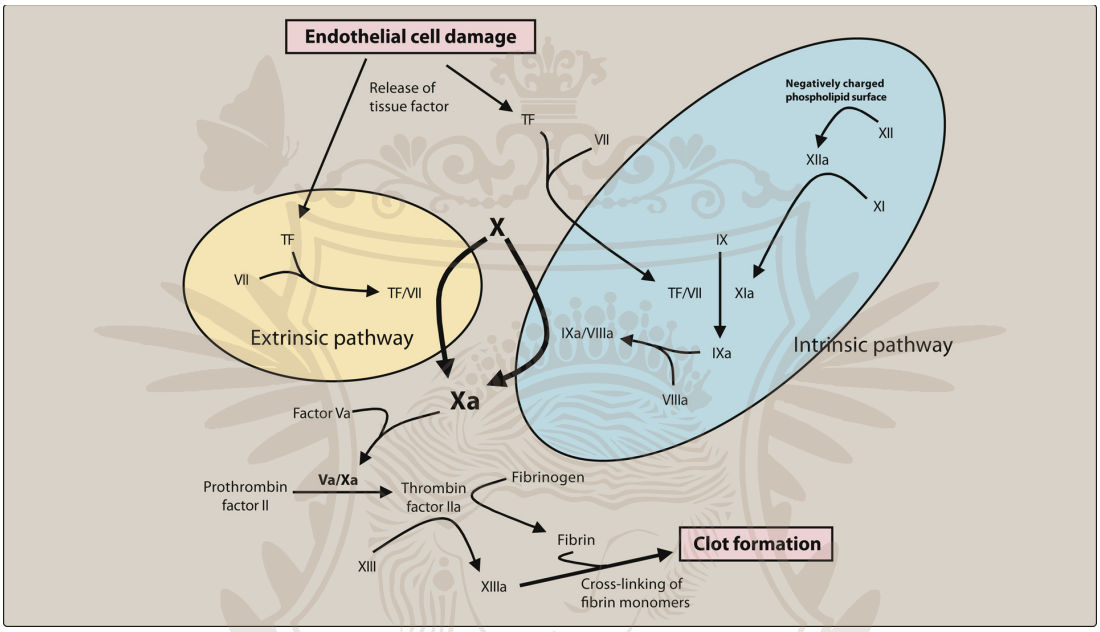

Figure 13.10 The clotting cascade.The extrinsic and intrinsic pathways are initiated by distinct mechanisms. They merge at the activation of factor X to form the common pathway. For all coagulation factors, the letter "a" denotes the activated form of the factor. TF = tissue factor.From J. S.Berek and D. L.Berek : *Berek & Novak's Gynecology*, 16th ed. Wolters Kluwer, (2020), Figure 33.1.

A. Formation of fibrin

Both the extrinsic and the intrinsic systems involve a cascade of enzyme reactions that sequentially transform various plasma factors (proenzymes) to their active (enzymatic) forms. [Note: The active form of a clotting factor is denoted by the letter "a."] Ultimately, factor Xa is produced, which converts prothrombin (factor II) to thrombin (factor IIa; Figure 13.11). Thrombin plays a key role in coagulation, because it is responsible for generation of fibrin, which forms the mesh-like

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matrix of the blood clot. If thrombin is not formed or if its function is impeded (for example, by antithrombin III), coagulation is inhibited.

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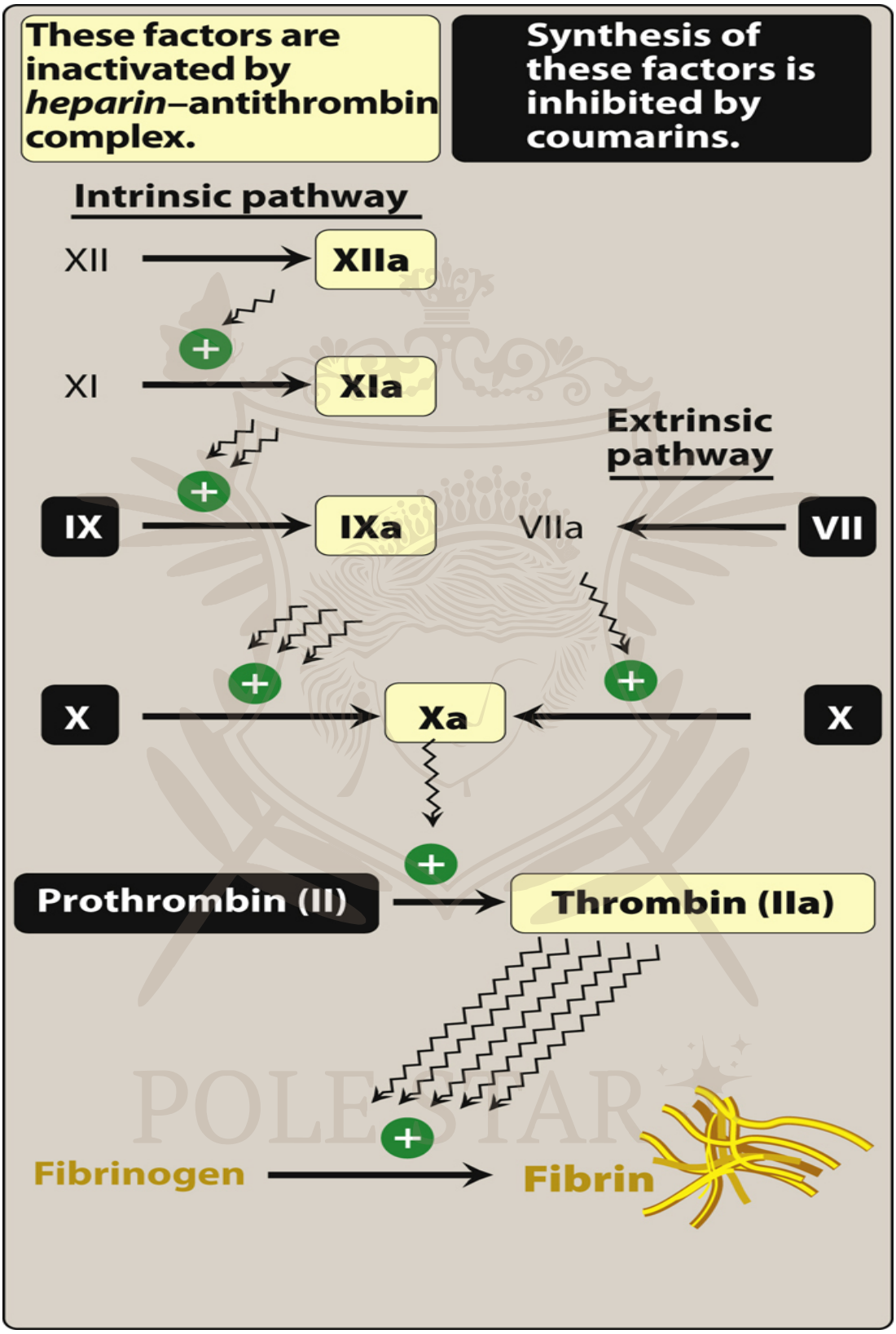

Figure 13.11 Formation of a fibrin clot.

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B. Inhibitors of coagulation

It is important that coagulation is restricted to the local site of vascular injury. Endogenously, protein C, protein S, antithrombin III, and tissue factor pathway inhibitor all inhibit coagulation factors as part of the body's natural effort to prevent local clots from becoming systemic following a vascular injury. The mechanism of action of several anticoagulant agents, including *heparin* and *heparin*-related products, involves activation of these endogenous inhibitors (primarily antithrombin III).

VI. PARENTERAL ANTICOAGULANTS

The anticoagulant drugs inhibit either the action of the coagulation factors (for example, *heparin*) or interfere with the synthesis of the coagulation factors (*warfarin*).

A. Heparin and low-molecular-weight heparins

Heparin [HEP-a-rin] is an injectable, rapid-acting anticoagulant that is often used acutely to interfere with the formation of thrombi. *Heparin* occurs naturally as a macromolecule complexed with histamine in mast cells, where its physiologic role is unknown. It is extracted for commercial use from porcine intestinal mucosa. Unfractionated *heparin* is a mixture of straight-chain, anionic glycosaminoglycans with a wide range of molecular weights. It is strongly acidic because of the presence of sulfate and carboxylic acid groups. The realization that low-molecular-weight forms of *heparin* (LMWHs) can also act as anticoagulants led to the isolation of *enoxaparin* [e-NOX-a-par-in] and *dalteparin* [DAL-te-PAR-in], produced by depolymerization of unfractionated *heparin.* The LMWHs are heterogeneous compounds about one-third the size of unfractionated *heparin*.

1.Mechanism of action: *Heparin* acts at a number of molecular targets, but its anticoagulant effect is a consequence of binding to antithrombin III, with the subsequent rapid inactivation of coagulation factors (Figure 13.12). Antithrombin III is an α globulin that inhibits serine proteases of thrombin (factor IIa) and factor Xa.

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In the absence of *heparin*, antithrombin III interacts very slowly with thrombin and factor Xa. When *heparin* molecules bind to antithrombin III, a conformational change occurs that catalyzes the inhibition of thrombin about 1000-fold. LMWHs complex with antithrombin III and inactivate factor Xa (including that located on platelet surfaces) but do not bind as avidly to thrombin. A unique pentasaccharide sequence contained in *heparin* and LMWHs permits their binding to antithrombin III (Figure 13.13).

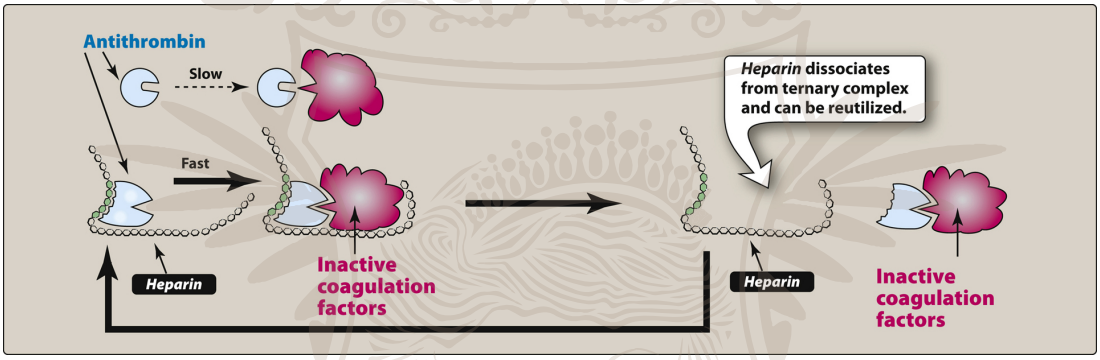

Figure 13.12 *Heparin* accelerates inactivation of coagulation factors by antithrombin.

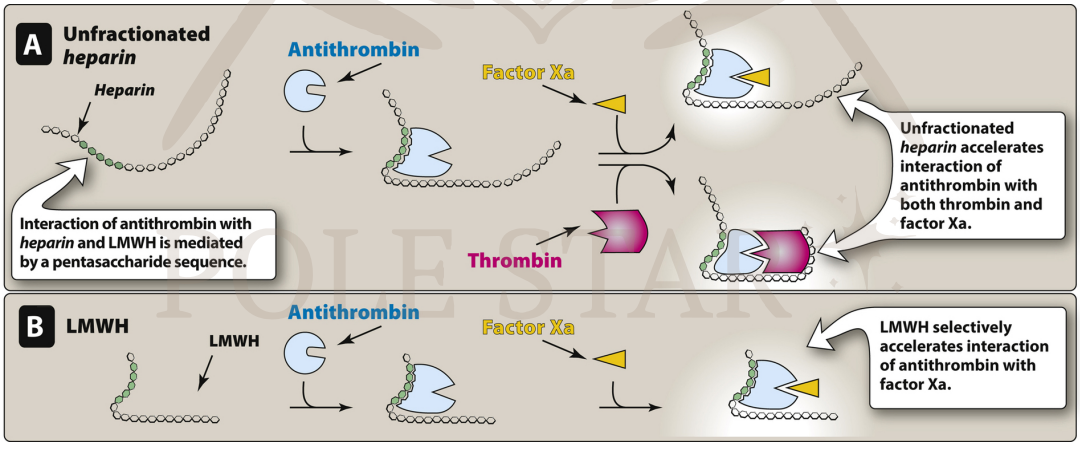

Figure 13.13 *Heparin*-mediated and low-molecular-weight heparin (LMWH)-mediated inactivation of thrombin or factor Xa.

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2.Therapeutic use: *Heparin* and the LMWHs limit the expansion of thrombi by preventing fibrin formation. These agents are used for the treatment of acute venous thromboembolism (DVT or PE). *Heparin* and LMWHs are also used for prophylaxis of postoperative venous thrombosis in patients undergoing surgery (for example, hip replacement) and those with acute MI. These drugs are the anticoagulants of choice for treating pregnant women, because they do not cross the placenta due to their large size and negative charge. LMWHs do not require the same intense monitoring as *heparin*, thereby saving laboratory costs and clinical staffing time. These advantages make LMWHs useful for both inpatient and outpatient therapy.

3.Pharmacokinetics: *Heparin* must be administered subcutaneously or intravenously, because the drug does not readily cross membranes (Figure 13.14). The LMWHs are usually administered subcutaneously. [Note: *Enoxaparin* can be administered intravenously in the treatment of MI.] *Heparin* is often initiated as an intravenous bolus to achieve immediate anticoagulation. This is followed by lower doses or continuous infusion of *heparin*, titrated to the desired level of anticoagulation according to the activated partial thromboplastin time (aPTT) or anti-Xa level. [Note: There is significant variability in sensitivity of the thromboplastin reagent used to perform aPTT laboratory testing. Therefore, the aPTT therapeutic range for *heparin* is institution specific.] The anticoagulant effect with *heparin* occurs within minutes of IV administration (or 1-2 hours after subcutaneous injection), whereas the maximum anti–factor Xa activity of the LMWHs occurs about 4 hours after subcutaneous injection. It is usually not necessary to monitor coagulation values with LMWHs because the plasma levels and pharmacokinetics of these drugs are more predictable. However, in renally impaired, pregnant, and obese patients, monitoring of factor Xa levels is recommended with LMWHs. In the blood, *heparin* binds to many proteins that neutralize its activity, causing unpredictable pharmacokinetics. *Heparin* binding to plasma proteins is variable in patients with thromboembolic diseases. Although generally restricted to the circulation, *heparin* is taken up by the

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monocyte/macrophage system, and it undergoes depolymerization and desulfation to inactive products. The inactive metabolites, as well as some of the parent *heparin,* undergo renal excretion. The LMWHs are primarily eliminated in the urine. Therefore, renal insufficiency prolongs the half-life of LMWH, and the dose of LMWH should be reduced in patients with renal impairment. The half-life of *heparin* is approximately 1.5 hours, whereas the half-life of the LMWHs is longer than that of *heparin*, ranging from 3 to 12 hours.

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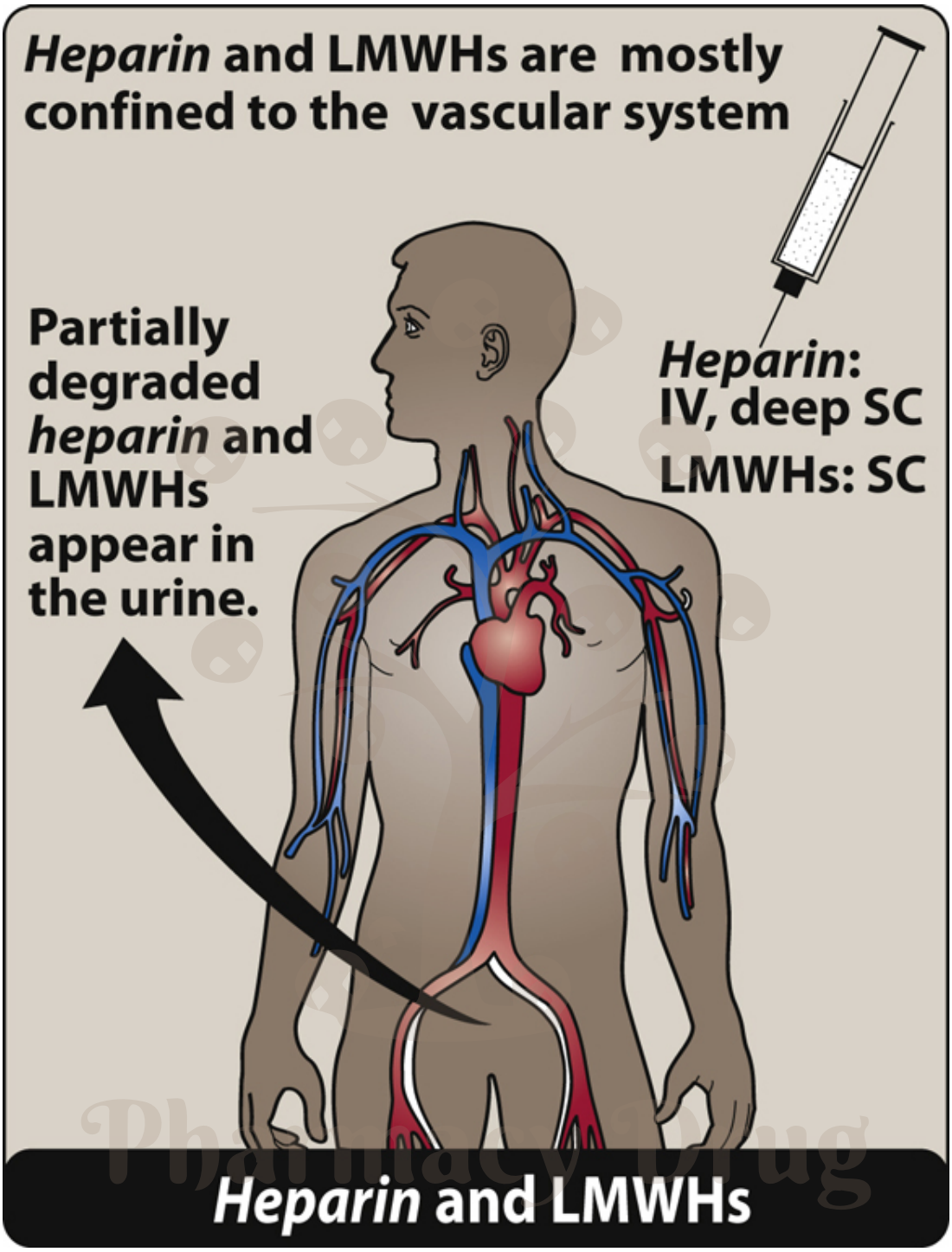

Figure 13.14 Administration and fate of *heparin* and low-molecular-weight heparins (LMWHs).

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4.Adverse effects: The chief complication of *heparin* and LMWH therapy is bleeding (Figure 13.15). Careful monitoring of the patient and laboratory parameters is required to minimize bleeding. Excessive bleeding may be managed by discontinuing the drug or by treating with *protamine sulfate.* When infused slowly, the latter combines ionically with *heparin* to form a stable, 1:1 inactive complex. It is important that the dosage of *protamine sulfate* is carefully titrated (1 mg for every 100 units of *heparin* administered), because *protamine sulfate* is a weak anticoagulant and excess amounts may trigger bleeding episodes or worsen bleeding potential. [Note: *Protamine sulfate* has incomplete anti-Xa neutralization of LMWH, although it can still be considered with bleeding due to LMWHs.] *Heparin* preparations are obtained from porcine sources and, therefore, may be antigenic. Possible adverse reactions include chills, fever, urticaria, and anaphylactic shock. *Heparin*-induced thrombocytopenia (HIT) is a serious condition, in which circulating blood contains an abnormally low number of platelets. This reaction is immune mediated and carries a risk of venous and arterial embolism. *Heparin* therapy should be discontinued when patients develop HIT or show severe thrombocytopenia. In cases of HIT, *heparin* can be replaced by another anticoagulant, such as *argatroban.* [Note: Patients who have experienced HIT with *heparin* may also have cross-sensitivity to LMWH, and LMWHs are not recommended in patients with HIT.] In addition, osteoporosis has been observed in patients on long-term *heparin* therapy. *Heparin* and LMWHs are contraindicated in patients who have hypersensitivity to *heparin*, bleeding disorders, a history of alcohol use disorder, or who have had recent surgery of the brain, eye, or spinal cord.

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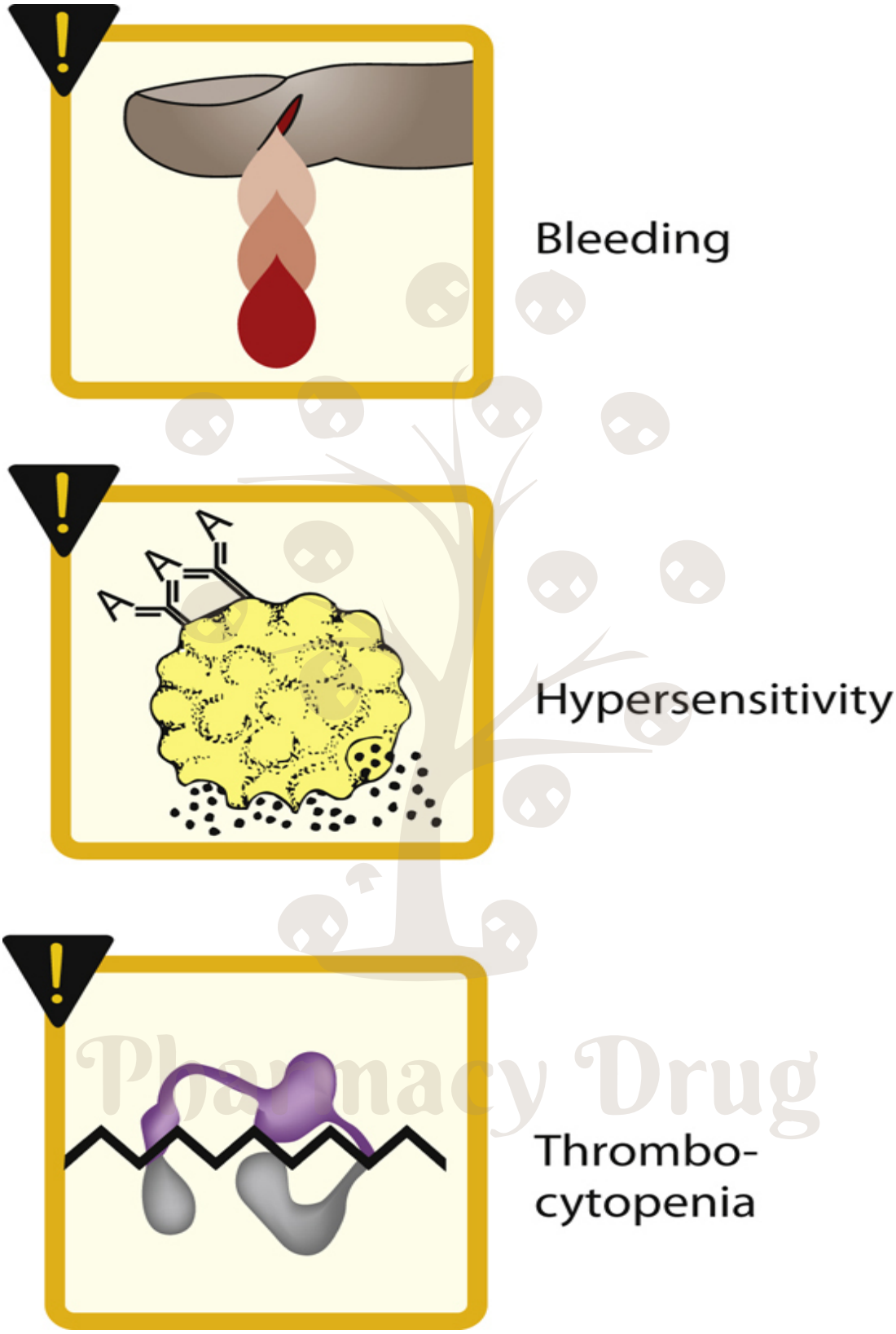

Figure 13.15 Adverse effects of *heparin*.

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B. Argatroban

Argatroban [ar-GA-troh-ban] is a synthetic parenteral anticoagulant that is derived from l-arginine. It is a direct thrombin inhibitor. *Argatroban* is used for the prophylaxis or treatment of venous thromboembolism in patients with HIT, and it is also approved for use during PCI in patients who have or are at risk for developing HIT. Anticoagulant effects are immediate. *Argatroban* is metabolized in the liver and has a half-life of about 39 to 51 minutes. Dose reduction is recommended for patients with hepatic impairment. Monitoring includes aPTT, hemoglobin, and hematocrit. As with other anticoagulants, the major side effect is bleeding.

C. Bivalirudin

Bivalirudin [bye-VAL-ih-ruh-din] is a parenteral anticoagulant that is an analog of hirudin, a thrombin inhibitor derived from saliva of the medicinal leech. It is a selective direct thrombin inhibitor that reversibly inhibits the catalytic site of both free and clot-bound thrombin. *Bivalirudin* is an alternative to *heparin* in patients undergoing PCI who have or are at risk for developing HIT and also in patients with unstable angina undergoing angioplasty. In patients with normal renal function, the half-life of *bivalirudin* is 25 minutes. Dosage adjustments are required in patients with renal impairment.

D. Fondaparinux

Fondaparinux [fawn-da-PARE-eh-nux] is a synthetically derived pentasaccharide anticoagulant that selectively inhibits factor Xa. By selectively binding to antithrombin III, *fondaparinux* potentiates (300- to 1,000-fold) the innate neutralization of factor Xa by antithrombin III. *Fondaparinux* is approved for use in the treatment of DVT and PE and for the prophylaxis of venous thromboembolism in the setting of orthopedic and abdominal surgery. The drug is well absorbed from the subcutaneous route with a predictable pharmacokinetic profile and, therefore, requires less laboratory monitoring than *heparin. Fondaparinux* is eliminated in the urine mainly as unchanged drug with an elimination half-life of 18 hours. It is contraindicated in patients with severe renal impairment. Bleeding is the major side effect of

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fondaparinux. There is no available agent for the reversal of bleeding associated with *fondaparinux.* HIT is less likely with *fondaparinux* than with *heparin*, but is still a possibility.

VII. VITAMIN K ANTAGONISTS

Coumarin anticoagulants owe their action to the ability to antagonize the cofactor functions of vitamin K. The only coumarin anticoagulant available in the United States is *warfarin* [WAR-far-in]. The international normalized ratio (INR) is the standard by which the anticoagulant activity of *warfarin* therapy is monitored. *Warfarin* has a narrow therapeutic index. Therefore, it is important that the INR is maintained within the optimal range and frequent monitoring may be required. [Note: The desired INR for most therapeutic uses is a range of 2.0 to 3.0, with higher INR values indicating a greater level of anticoagulation.]

A. Warfarin

1.Mechanism of action: Factors II, VII, IX, and X (Figure 13.11) require vitamin K as a cofactor for their synthesis by the liver. These factors undergo vitamin K–dependent posttranslational modification, whereby a number of their glutamic acid residues are carboxylated to form γ-carboxyglutamic acid residues (Figure 13.16). The γ-carboxyglutamyl residues bind calcium ions, which are essential for interaction between the coagulation factors and platelet membranes. In the carboxylation reactions, the vitamin K–dependent carboxylase fixes CO_2 to form the new COOH group on glutamic acid. The reduced vitamin K cofactor is converted to vitamin K epoxide during the reaction. Vitamin K is regenerated from the epoxide by vitamin K epoxide reductase, the enzyme that is inhibited by *warfarin. Warfarin* treatment results in the production of clotting factors with diminished activity (10% to 40% of normal), due to the lack of sufficient γ-carboxyglutamyl side chains. Unlike *heparin*, the anticoagulant effects of *warfarin* are not observed immediately after drug administration. Instead, peak effects may be delayed for 72 to 96 hours, which is the time required to deplete the pool of circulating clotting factors. [Note: During initiation of *warfarin* therapy, it may be necessary to overlap

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warfarin with another anticoagulant, such as *heparin* or LMWH. This is often referred to as “bridging” and is used in patients with high thromboembolic risk.] The anticoagulant effects of *warfarin* can be overcome by the administration of *vitamin K.* However, reversal following administration of *vitamin K* takes approximately 24 hours (the time necessary for degradation of already synthesized clotting factors).

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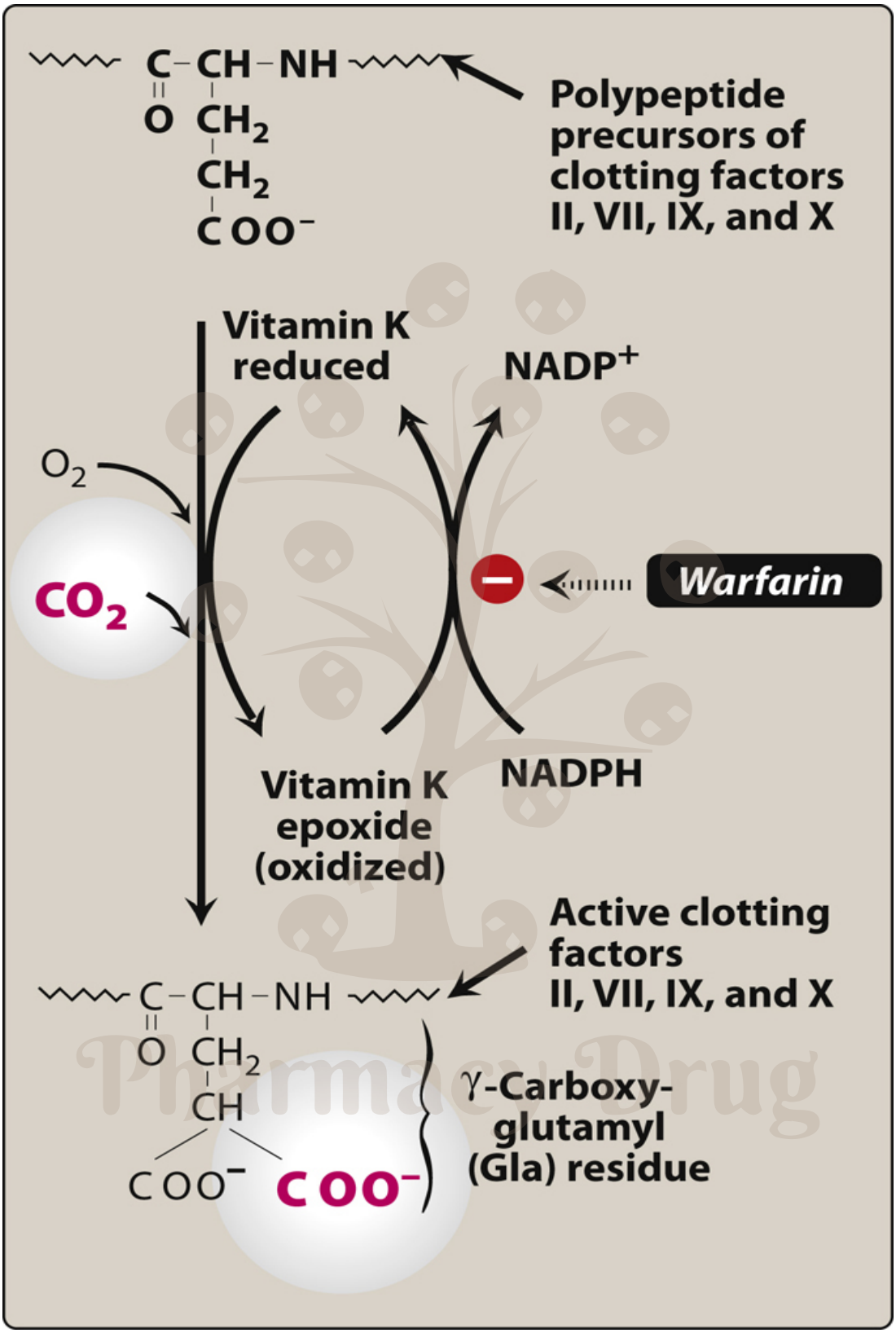

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Figure 13.16 Mechanism of action of *warfarin*.$NADP^+$ = oxidized form of nicotinamide adenine dinucleotide phosphate; NADPH = reduced form of nicotinamide adenine dinucleotide phosphate.

2.Therapeutic use: *Warfarin* is used in the prevention and treatment of DVT and PE, stroke prevention in the setting of atrial fibrillation and/or prosthetic heart valves, protein C and S deficiency, and antiphospholipid syndrome. It is also used for prevention of venous thromboembolism following orthopedic surgery.

3.Pharmacokinetics: *Warfarin* is rapidly absorbed after oral administration (100% bioavailability with little individual patient variation). *Warfarin* is highly bound to plasma albumin, which prevents its diffusion into the cerebrospinal fluid, urine, and breast milk. However, drugs that have a greater affinity for the albumin-binding site, such as sulfonamides, can displace the anticoagulant and lead to a transient, elevated activity. Drugs that affect *warfarin* binding to plasma proteins can lead to variability in the therapeutic response to *warfarin. Warfarin* readily crosses the placental barrier. The mean half-life of *warfarin* is approximately 40 hours, but this value is highly variable among individuals. *Warfarin* is metabolized by the CYP450 system (mainly CYP2C9) to inactive components. After conjugation to glucuronic acid, the inactive metabolites are excreted in urine and feces. Agents that affect the metabolism of *warfarin* may alter its therapeutic effects. *Warfarin* has numerous drug and food interactions that may potentiate or attenuate its anticoagulant effect. [Note: Food interactions may include vitamin K–containing products such as green leafy vegetables, nutritional supplements, and grapefruit. It is important to counsel patients to be consistent with their diet to prevent changes in drug levels.] The list of interacting drugs is extensive. A summary of some of the important interactions is shown in Figure 13.17.

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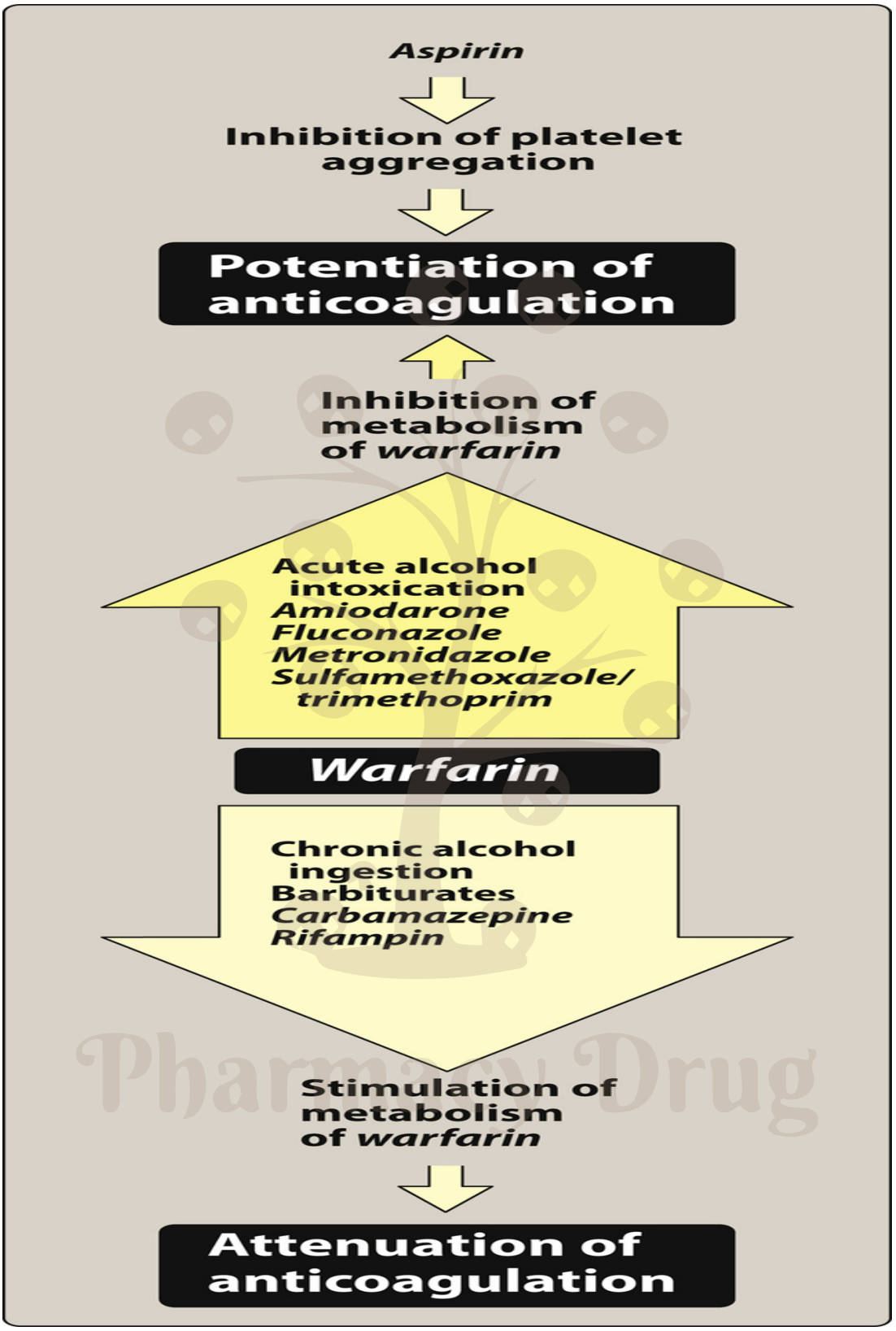

Figure 13.17 Drugs affecting the anticoagulant effect of *warfarin*.

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4.Adverse effects: The principal adverse effect of *warfarin* is bleeding. Minor bleeding may be treated by withdrawal of the drug or administration of oral *vitamin K*, but severe bleeding may require greater doses of *vitamin K* given intravenously. Whole blood, frozen plasma, and plasma concentrates of blood factors may also be used for rapid reversal of *warfarin.* Skin lesions and necrosis are rare complications of *warfarin* therapy. Purple toe syndrome, a rare, painful, blue-tinged discoloration of the toe caused by cholesterol emboli from plaques, has also been observed with *warfarin* therapy. *Warfarin* is teratogenic and is contraindicated in pregnancy.

VIII. DIRECT ORAL ANTICOAGULANTS

A. Dabigatran

1.Mechanism of action: *Dabigatran etexilate* [da-bi-GAT-ran e-TEX-i-late] is the prodrug of the active moiety *dabigatran*, which is an oral direct thrombin inhibitor. Both clot-bound thrombin and free thrombin are inhibited by *dabigatran*.

2.Therapeutic use: *Dabigatran* is approved for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. It may also be used in the treatment of DVT and PE in patients who have already received parenteral anticoagulants and as prophylaxis to prevent or reduce the risk of recurrence of DVT and PE. The drug is contraindicated in patients with mechanical prosthetic heart valves and is not recommended in patients with bioprosthetic heart valves.

3.Pharmacokinetics: *Dabigatran etexilate* is administered orally. It is hydrolyzed to the active drug, *dabigatran*, by various plasma esterases. *Dabigatran* is metabolized by esterases. It is a substrate for P-glycoprotein (P-gp) and is eliminated renally.

4.Adverse effects: The major adverse effect, like other anticoagulants, is bleeding. *Dabigatran* should be used with caution in renal impairment or in patients over the age of 75 years,

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as the risk of bleeding is higher in these groups. *Idarucizumab* may be used to reverse bleeding in emergent cases with severe bleeding. GI adverse effects are common with *dabigatran* and may include dyspepsia, abdominal pain, esophagitis, and GI bleeding. Abrupt discontinuation should be avoided, as patients may be at increased risk for thrombotic events.

B. Direct oral factor Xa inhibitors

1.Mechanism of action: *Apixaban* [a-PIX-a-ban], *edoxaban* [e-DOX-a-ban], and *rivaroxaban* [RIV-a-ROX-a-ban] are oral inhibitors of factor Xa. Inhibition of factor Xa reduces the production of thrombin (IIa) from prothrombin (Figure 13.11).

2.Therapeutic use: These agents are approved for prevention of stroke in nonvalvular atrial fibrillation, as well as the treatment of DVT and PE. *Rivaroxaban* and *apixaban* are also used as prophylaxis to prevent or reduce the risk of recurrence of DVT and PE. In addition, *rivaroxaban* can be used to prevent major cardiovascular events associated with coronary artery disease or peripheral artery disease.

3.Pharmacokinetics: These drugs are adequately absorbed after oral administration. *Rivaroxaban* is metabolized by the CYP 3A4/5 and CYP 2J2 isoenzymes to inactive metabolites. About one-third of the drug is excreted unchanged in the urine, and the inactive metabolites are excreted in the urine and feces. *Apixaban* is primarily metabolized by CYP 3A4, with CYP enzymes 1A2, 2C8, 2C9, 2C19, and 2J2 all sharing minor metabolic roles; approximately 27% is excreted renally. *Edoxaban* is mainly metabolized by hydrolysis and is eliminated primarily unchanged in the urine. All of these drugs are substrates of P-gp, and dosages should be reduced (in some cases concomitant use should be avoided) with P-gp inhibitors such as *clarithromycin*, *verapamil*, and *amiodarone.* Concomitant administration of *apixaban* and *rivaroxaban* with drugs that are strong P-gp and CYP 3A4 inducers (for example, *phenytoin*, *carbamazepine*, *rifampin*, *St. John's wort*) should be avoided due to the potential for reduced efficacy of the factor Xa inhibitors.

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4.Adverse effects: Bleeding is the most serious adverse effect. Factor Xa may be used to reverse serious bleeding caused by *apixaban* and *rivaroxaban.* Declining kidney function can prolong the effect of these drugs and, therefore, increase the risk of bleeding. Renal dosage adjustments are recommended for these agents. Abrupt discontinuation of the factor Xa inhibitors should be avoided due to an increased risk for thrombotic events.

Clinical Application 13.2: Transitioning From Warfarin to Direct Oral Factor Xa Inhibitors

As direct oral factor Xa inhibitors become a more cost-effective option for patients, the situation will present itself when a patient would like to transition from *warfarin* to these agents. There may be several reasons why a patient is a better candidate for direct oral factor Xa inhibitors, such as likelihood of poor INR control, difficulty monitoring the INR, and dangerous fluctuations in the INR. The strategy for transitioning from *warfarin* to direct oral factor Xa inhibitors differs for each medication. When switching from *warfarin* to *apixaban*, the INR should be less than 2. *Edoxaban* can be started when the INR is 2.5 or less. *Rivaroxaban* should be started when the INR is less than 3. Therefore, close monitoring of the INR is important during the transition period to ensure the patient is not at increased risk of bleeding.

IX. THROMBOLYTIC DRUGS

Acute thromboembolic disease in selected patients may be treated by the administration of drugs that activate the conversion of plasminogen to plasmin, a serine protease that hydrolyzes fibrin and, thus, dissolves clots.

A. Common characteristics of thrombolytic agents

1.Mechanism of action: The thrombolytic agents act either directly or indirectly to convert plasminogen to plasmin, which, in turn, cleaves fibrin, thus lysing thrombi (Figure 13.18). Clot dissolution and reperfusion occur with a higher frequency when therapy is initiated early after clot formation because clots become more resistant to lysis as they age. Unfortunately, increased local thrombi may occur as the clot dissolves, leading to enhanced

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platelet aggregation and thrombosis. Strategies to prevent this include administration of antiplatelet drugs, such as *aspirin*, or antithrombotic agents, such as *heparin*.

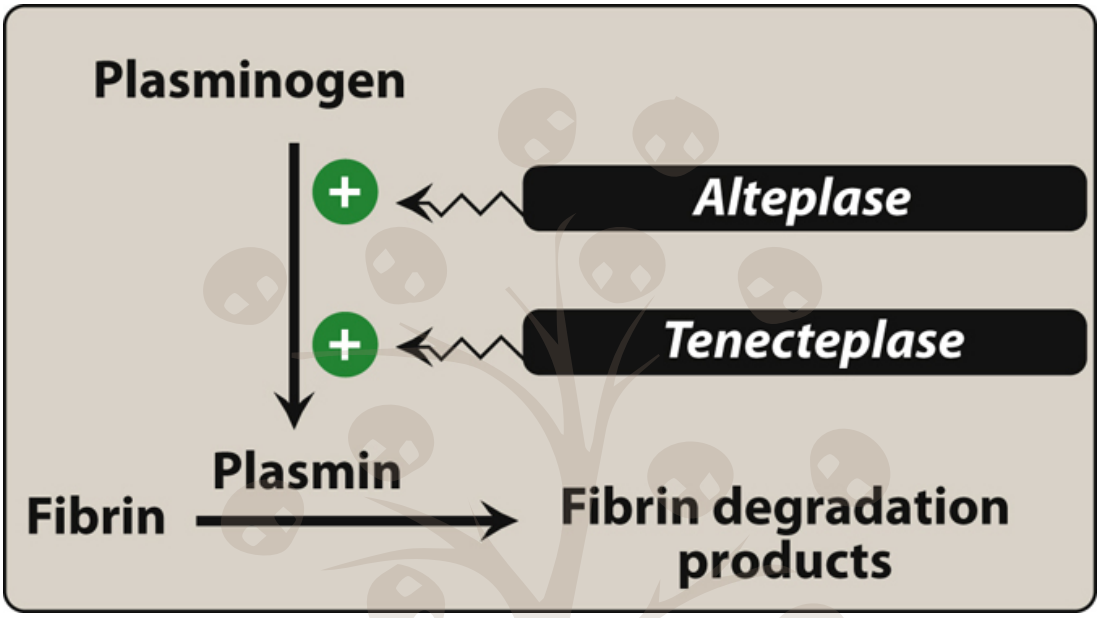

Figure 13.18 Activation of plasminogen by thrombolytic drugs.

2.Therapeutic use: Originally used for the treatment of DVT and serious PE, thrombolytic drugs are now used less frequently because of the tendency to cause serious bleeding. For MI, intracoronary delivery of the drugs is the most reliable in terms of achieving recanalization. However, cardiac catheterization may not be possible in the 2- to 6-hour "therapeutic window," beyond which significant myocardial salvage becomes less likely. Thus, thrombolytic agents are usually administered intravenously. Thrombolytic agents are helpful in restoring catheter and shunt function, by lysing clots causing occlusions. They are also used to dissolve clots that result in strokes.

3.Adverse effects: Thrombolytic agents do not distinguish between the fibrin of an unwanted thrombus and the fibrin of a beneficial hemostatic plug. Thus, hemorrhage is a major adverse effect. For example, a previously unsuspected lesion, such as a

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gastric ulcer, may hemorrhage following injection of a thrombolytic agent (Figure 13.19). These drugs are contraindicated in pregnancy and in patients with healing wounds, a history of cerebrovascular accident, brain tumor, head trauma, intracranial bleeding, and metastatic cancer.

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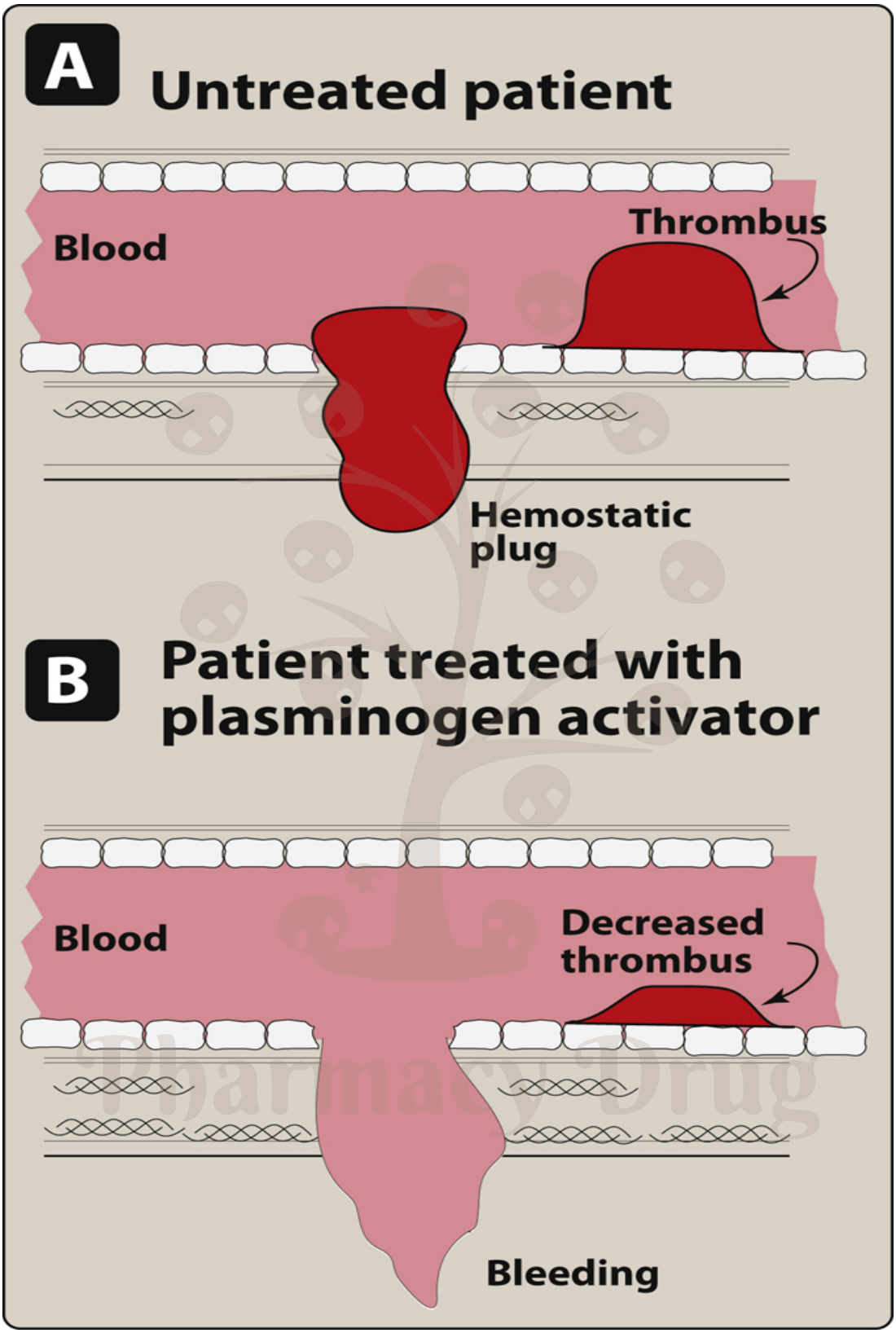

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Figure 13.19 Degradation of an unwanted thrombus and a beneficial hemostatic plug by plasminogen activators.

B. Fibrinolytic agents

Alteplase [AL-teh-plase] (formerly known as *tissue plasminogen activator* or *tPA*) is a serine protease originally derived from cultured human melanoma cells. It is now obtained as a product of recombinant DNA technology. *Tenecteplase* [ten-EK-te-plase] is recombinant tPA with a longer half-life and greater binding affinity for fibrin than *alteplase. Alteplase* has a low affinity for free plasminogen in the plasma, but it rapidly activates plasminogen that is bound to fibrin in a thrombus or a hemostatic plug. Thus, *alteplase* is said to be "fibrin selective" at low doses. *Reteplase* [RE-te-plase] is another available agent in this class that is considered fibrin specific. *Alteplase* is approved for the treatment of MI, massive PE, and acute ischemic stroke. *Reteplase and tenecteplase* are only approved for use in acute MI. *Alteplase* has a very short half-life (5-30 minutes), and therefore, a portion of the total dose is injected intravenously as a bolus and the remaining drug is administered over 1 to 3 hours, depending on the indication. *Reteplase* has a slightly longer half-life and is considered comparable with *alteplase*, but it is easier to use since it can be given as two intravenous boluses about 30 minutes apart. *Tenecteplase* has a longer half-life and, therefore, may be administered as an intravenous bolus. *Alteplase* may cause angioedema, and there may be an increased risk of this effect when combined with angiotensin-converting enzyme (ACE) inhibitors. *Tenecteplase* and *reteplase* are usually preferred over *alteplase* because of their more favorable benefit-to-risk profile and ease of use.

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X. DRUGS USED TO TREAT BLEEDING

Bleeding problems may have their origin in naturally occurring pathologic conditions, such as hemophilia, or as a result of fibrinolytic states that may arise after surgery. The use of anticoagulants may also give rise to hemorrhage. Certain natural proteins and *vitamin K*, as well as synthetic antagonists, are effective in controlling this bleeding (Figure 13.20).

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Concentrated preparations of coagulation factors are available from human donors. However, these preparations carry the risk of transferring viral infections. Blood transfusion is also an option for treating severe hemorrhage.

Antidote	Reason for Bleeding	Adverse Effects	Monitoring Parameters
Aminocaproic acid *Tranexamic acid*	Fibrinolytic state	Muscle necrosis Thrombosis CVA Seizure	CBC Muscle enzymes Blood pressure
Factor Xa	*Apixaban, Rivaroxaban*	Thrombosis MI	None necessary per the manufacturer
Idarucizumab	*Dabigatran*	Hypokalemia Thrombosis	aPTT Clotting time Thrombin time
Protamine sulfate	*Heparin*	Flushing Nausea/vomiting Dyspnea Bradyarrhythmia Hypotension Anaphylaxis	Coagulation monitoring Blood pressure Heart rate
Vitamin K1	*Warfarin*	Skin reaction Anaphylaxis	PT/INR

Figure 13.20 Summary of drugs used to treat bleeding.aPTT = activated partial thromboplastin time, CBC = complete blood count, CVA = cerebrovascular accident, INR = international normalized ratio, MI = myocardial infarction, PT = prothrombin time.

A. Aminocaproic acid and tranexamic acid

Bleeding can be controlled by the administration of *aminocaproic* [a-mee-noe-ka-PROE-ic] *acid* or *tranexamic* [tran-ex-AM-ic] *acid.* Both agents are synthetic, orally active, excreted in the urine, and inhibit plasminogen activation. *Tranexamic acid* is 10 times more potent than *aminocaproic acid.* A potential side effect is intravascular thrombosis.

B. Protamine sulfate

Protamine [PROE-ta-meen] *sulfate* antagonizes the anticoagulant effects of *heparin.* This protein is derived from fish sperm or testes and is high in arginine content, which explains its basicity. The positively charged *protamine* interacts with the negatively charged *heparin*, forming a stable complex without anticoagulant activity. Adverse effects of drug administration include hypersensitivity as well

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as dyspnea, flushing, bradycardia, and hypotension when rapidly injected.

C. Vitamin K

Vitamin K $_1$ (*phytonadione*) administration can stop bleeding problems due to *warfarin* by increasing the supply of active *vitamin K* $_1$, thereby inhibiting the effect of *warfarin. Vitamin K* $_1$ may be administered via the oral, subcutaneous, or intravenous route. [Note: Intravenous *vitamin K* should be administered by slow IV infusion to minimize the risk of hypersensitivity or anaphylactoid reactions.] For the treatment of bleeding, the subcutaneous route of *vitamin K* $_1$ is less preferred, as it is not as effective as oral or IV administration. The response to *vitamin K* $_1$ is slow, requiring about 24 hours to reduce INR (time to synthesize new coagulation factors). Thus, if immediate hemostasis is required, fresh frozen plasma should be infused.

D. Idarucizumab

Idarucizumab [EYE-da-roo-KIZ-ue-mab] is a monoclonal antibody fragment used to reverse bleeding caused by *dabigatran.* By binding to *dabigatran* and its metabolites, *idarucizumab* neutralizes anticoagulation. *Idarucizumab* is administered intravenously and is rapidly eliminated. *Idarucizumab* is used in emergency situations, in the inpatient setting. Because it reverses the effect of *dabigatran*, thrombosis is the most serious adverse effect of *idarucizumab*.

E. Factor Xa

Factor Xa [FAK-tor 10-a] is a recombinant modified human protein administered parenterally for the reversal of *apixaban* or *rivaroxaban* in the setting of life-threatening or uncontrolled bleeding. *Factor Xa* binds to *apixaban* or *rivaroxaban* to prevent inhibition of Factor Xa, thereby reversing the anticoagulant effect of these agents. *Factor Xa* is not approved for *edoxaban* reversal. *Factor Xa* is associated with serious and life-threatening adverse events including arterial and venous thromboembolism, myocardial infarction, ischemic stroke, cardiac arrest, and sudden death. In order to reduce thromboembolic risk, *apixaban* or *rivaroxaban* should be resumed as soon as medically appropriate after treatment with *Factor Xa*.

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CHAPTER SUMMARY

- The body naturally creates clots to help prevent blood loss and maintain hemostasis in response to physical trauma. Thrombi and emboli are developed similarly but are triggered by a pathologic condition in the vascular system. Thrombi and emboli may occlude blood vessels, and this can be life threatening if not treated appropriately.
- *Aspirin* inhibits thromboxane A_2 synthesis by acetylation of a serine residue on the active site of COX-1.
- $P2Y_{12}$ receptor antagonists (*clopidogrel*, *prasugrel*, *ticagrelor*, and *cangrelor*) inhibit the binding of ADP to the $P2Y_{12}$ receptor on platelets, thereby inhibiting the activation of the GP IIb/IIIa receptors.
- Glycoprotein IIb/IIIa inhibitors (*eptifibatide* and *tirofiban*) inhibit the GP IIb/IIIa receptor complex from forming and thus inhibit platelet aggregation. These medications are administered intravenously as an adjunct to PCI for the prevention of cardiac ischemic complications.
- *Heparin* is an injectable, rapid-acting anticoagulant that is used acutely to interfere with the formation of thrombi. Both *heparin* and the LMWHs limit the expansion of thrombi by preventing fibrin formation. These agents are used for the treatment and prophylaxis of DVT or PE.
- *Warfarin* is a vitamin K antagonist and is monitored using the INR. *Warfarin* requires frequent monitoring to ensure the INR is kept within therapeutic range. It is used in the prevention and treatment of DVT and PE, stroke prevention in the setting of atrial fibrillation and/or mechanical and prosthetic heart valves, protein C and S deficiency, and antiphospholipid syndrome.
- Direct oral anticoagulants include *dabigatran*, which is an oral direct thrombin inhibitor, and the factor Xa inhibitors, which include *apixaban*, *edoxaban*, and *rivaroxaban.* These medications are used for the prevention of stroke in nonvalvular atrial fibrillation and prevention or treatment of DVT and PE.
- Thrombolytic agents (*alteplase*, *reteplase*, and *tenecteplase*) are used for restoring catheter and shunt function by lysing clots causing occlusions.
- *Heparin*, LMWHs, *warfarin*, fibrinolytics, and the direct oral anticoagulants can all increase the risk of bleeding and, in some instances, can cause life-threatening hemorrhage. Available reversal agents are *aminocaproic acid*, *tranexamic acid*, *idarucizumab*, *protamine sulfate*, *vitamin K1*, and *factor Xa.*

STUDY QUESTIONS

Choose the ONE best answer.

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13.1 A patient is being discharged from the hospital after having a myocardial infarction. The patient will be discharged on aspirin and clopidogrel. Which medication should be avoided while the patient is taking clopidogrel?

A. Omeprazole
B. Lisinopril
C. Atorvastatin
D. Famotidine

Correct answer = A. Clopidogrel is a prodrug that must be metabolized by CYP2C19 to its active metabolite, in order to achieve therapeutic efficacy. Drugs such as omeprazole and esomeprazole should be avoided while taking clopidogrel because they inhibit CYP2C19, preventing clopidogrel from being metabolized to the active form. The other drugs listed do not have significant drug interactions with clopidogrel.

13.2 A 54-year-old man presents to the emergency department with chest pain. He is diagnosed with unstable angina. Which antiplatelet agent should be avoided in this patient?

A. Clopidogrel
B. Cilostazol
C. Aspirin
D. Dipyridamole

Correct answer = D. Dipyridamole should be avoided in patients with unstable angina. Dipyridamole has vasodilating properties, which may worsen ischemia, otherwise known as the coronary steal phenomenon.

13.3 A pregnant patient presents to clinic with a right calf that is tender, red, painful, and warm to the touch. She is diagnosed with deep venous thrombosis and requires anticoagulation. What is the anticoagulant of choice for treating this patient?

A. Warfarin
B. Enoxaparin
C. Apixaban
D. Rivaroxaban

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Correct answer = B. Heparin and LMWHs are the drugs of choice for treating pregnant women. These medications do not cross the placenta due to their large size and negative charge and will not cause harm to the fetus. Warfarin is teratogenic, crosses the placenta, and fetal plasma concentrations are similar to maternal values. The use of apixaban and rivaroxaban is not recommended as data are limited and insufficient to determine risks of major birth defects, miscarriage, or adverse developmental outcomes.

13.4 Monitoring of anti-Xa levels for patients taking LMWH is recommended in patients with which of the following conditions?

A. Asplenia
B. Renal impairment
C. Hypothyroidism
D. Hepatic impairment

Correct answer = B. Monitoring of anti-Xa levels for patients taking LMWH is typically not recommended because the plasma levels and pharmacokinetics of these drugs are more predictable as compared with heparin. However, monitoring is recommended in renal impairment, pregnancy, or obesity. LMWH is primarily excreted in the urine; therefore, renal insufficiency prolongs the half-life of LMWH and the dose of LMWH may need to be adjusted in patients with renal impairment.

13.5 A patient has atrial fibrillation and is being treated with warfarin. What monitoring parameter is most appropriate to assess the effectiveness of the treatment?

A. Hemoglobin
B. aPTT
C. Thrombin time
D. INR

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Correct answer = D. Warfarin is monitored by measuring the INR. Although it may be pertinent to monitor hemoglobin while a patient is taking warfarin, this is not used to assess treatment with warfarin. Thrombin time and aPTT can be used to monitor other anticoagulants but not warfarin.

13.6 Which medication may increase the anticoagulation effect of warfarin?

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A. Amiodarone
B. Rifampin
C. Carbamazepine
D. Phenobarbital

Correct answer = A. Amiodarone may increase the anticoagulation effect of warfarin. Other medications that may increase warfarin's effect include fluconazole, metronidazole, and sulfamethoxazole/trimethoprim. Rifampin, carbamazepine, and phenobarbital all may decrease the anticoagulation effect of warfarin.

13.7 A 32-year-old patient is started on a new anticoagulant during his hospital visit. The patient has a mechanical heart valve. Which anticoagulant was most likely started for this patient?

A. Apixaban
B. Warfarin
C. Dabigatran
D. Rivaroxaban

Correct answer = B. Warfarin is the only anticoagulant indicated for use in patients with mechanical prosthetic heart valves. Dabigatran, apixaban, rivaroxaban, and edoxaban are not approved for use in patients with mechanical heart valves.

13.8 A patient is taking rivaroxaban for stroke prevention in the setting of atrial fibrillation. She is going to start verapamil for rate control. Which of the following statements is CORRECT?

A. This patient should double the dose of rivaroxaban after starting verapamil.
B. The addition of verapamil may increase the patient's risk of bleeding.
C. Rivaroxaban concentration will decrease when taken with verapamil.
D. The starting dose of verapamil should be increased since rivaroxaban is an inducer.

Correct answer = B. Verapamil is a P-gp-inhibitor. Rivaroxaban is a substrate for P-gp, and when taken with verapamil, concentrations can increase, thereby increasing the risk of bleeding. Since verapamil is an inhibitor of P-gp, rather than an inducer, we

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would expect rivaroxaban concentrations to increase rather than decrease. Hence, there is no reason to double the dose of rivaroxaban. Finally, rivaroxaban is a substrate of P-gp; it is neither an inducer nor an inhibitor of P-gp.

13.9 A 56-year-old patient who is prescribed dabigatran is admitted to the hospital with an intracranial hemorrhage. Which agent can be used to reverse bleeding?

A. Idarucizumab
B. Vitamin K
C. Factor Xa
D. Protamine sulfate

Correct answer = A. Idarucizumab is used to reverse bleeding caused by dabigatran. Vitamin K is used for bleeding associated with warfarin. Factor Xa is used to reverse bleeding caused by apixaban or rivaroxaban. Protamine sulfate is used to reverse bleeding caused by heparin.

13.10 Which of the following statements is correct regarding ticagrelor?

A. It inhibits thromboxane A_2 synthesis.
B. It inhibits the GP IIb/IIIa receptor complex.
C. It irreversibly inhibits the binding of ADP to $P2Y_{12}$ receptor on platelets.
D. It reversibly inhibits the binding of ADP to $P2Y_{12}$ receptor on platelets.

Correct answer = D. Ticagrelor reversibly binds to the $P2Y_{12}$ ADP receptor. Clopidogrel and prasugrel irreversibly bind to the $P2Y_{12}$ ADP receptor. Aspirin inhibits thromboxane A_2 synthesis by acetylation of a serine residue on the active site of COX-1. Eptifibatide and tirofiban inhibit the GP IIb/IIIa receptor complex.

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14

Drugs for Hyperlipidemia

Christina E. DeRemer, Eric Dietrich

I. OVERVIEW

Coronary heart disease (CHD) is the leading cause of death worldwide. CHD is correlated with abnormal cholesterol levels (dyslipidemia). Specifically, CHD is associated with elevated levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides and low levels of high-density lipoprotein cholesterol (HDL-C). Other risk factors for CHD include cigarette smoking, hypertension, obesity, diabetes, chronic kidney disease, and advanced age. Elevated cholesterol levels (hyperlipidemia) may be due to lifestyle factors (for example, lack of exercise or diet containing excess saturated fats). Hyperlipidemia can also result from an inherited defect in lipoprotein metabolism or, more commonly, from a combination of genetic and lifestyle factors. Appropriate lifestyle changes, along with antihyperlipidemic drug therapy, can lead to a substantial reduction in CHD mortality. Antihyperlipidemic drugs (Figure 14.1) are often taken indefinitely to reduce the risk of atherosclerotic cardiovascular disease (ASCVD) in select patients and to control plasma lipid levels. [Note: ASCVD includes CHD (myocardial infarction, also known as a "heart attack," and angina), stroke, and peripheral artery disease.] Figure 14.2 illustrates the normal metabolism of serum lipoproteins and the characteristics of the major genetic hyperlipidemias.

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HMG CoA REDUCTASE INHIBITORS (STATINS)

Atorvastatin LIPITOR
Fluvastatin LESCOL
Lovastatin ALTOPREV
Pitavastatin LIVALO
Pravastatin PRAVACHOL
Rosuvastatin CRESTOR
Simvastatin ZOCOR

CHOLESTEROL ABSORPTION INHIBITOR

Ezetimibe ZETIA

BILE ACID SEQUESTRANTS

Colesevelam WELCHOL
Colestipol COLESTID
Cholestyramine PREVALITE, QUESTRAN

PCSK9 INHIBITORS

Alirocumab PRALUENT
Evolocumab REPATHA

ACL INHIBITOR

Bempedoic Acid NEXLETOL

MTP INHIBITOR

Lomitapide JUXTAPID

FIBRATES

Gemfibrozil LOPID
Fenofibrate TRICOR, TRIGLIDE

NIACIN

Niacin NIASPAN, SLO-NIACIN

OMEGA-3 FATTY ACIDS

Docosahexaenoic and *eicosapentaenoic acids* LOVAZA, VARIOUS OTC PREPARATIONS
Icosapent ethyl VASCEPA

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Figure 14.1 Summary of antihyperlipidemic drugs.ACL = adenosine triphosphate-citrate lyase; HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A; MTP = microsomal triglyceride transfer protein; OTC = over-the-counter; PCSK9 = proprotein convertase subtilisin kexin type 9.

POLE STAR

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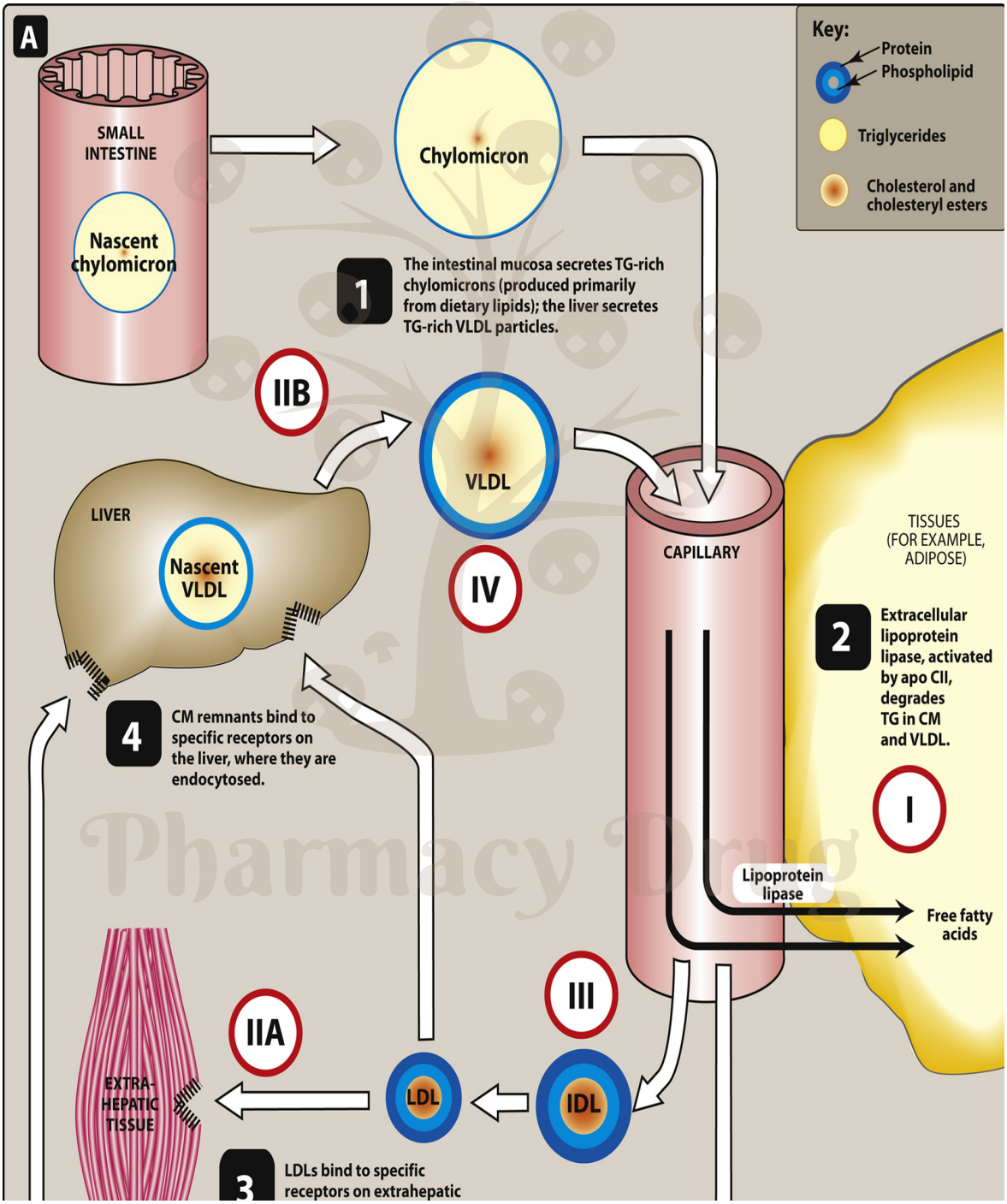

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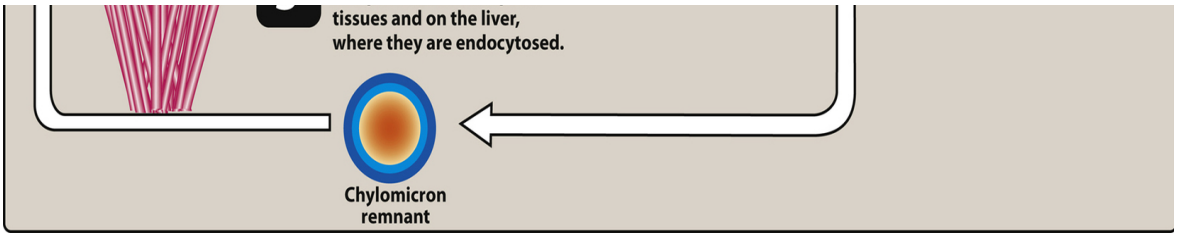
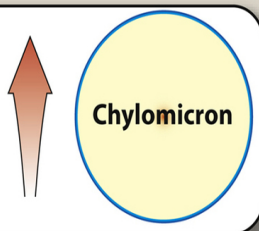


B

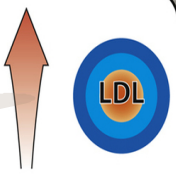
Type I (FAMILIAL HYPERCHYLOMICRONEMIA)

- Massive fasting hyperchylomicronemia, even following normal dietary fat intake, resulting in greatly elevated serum TG levels.
- Deficiency of lipoprotein lipase or deficiency of normal apolipoprotein CII (rare).
- Type I is not associated with an increase in coronary heart disease.
- Treatment: Low-fat diet. No drug therapy is effective for Type I hyperlipidemia.



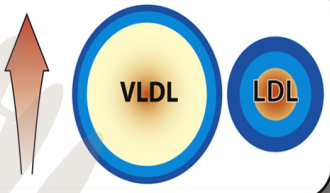
Type IIA (FAMILIAL HYPERCHOLESTEROLEMIA)

- Elevated LDL with normal VLDL levels due to a block in LDL degradation. This results in increased serum cholesterol but normal TG levels.
- Caused by defects in the synthesis or processing of LDL receptors.
- Ischemic heart disease is greatly accelerated.
- Treatment: Diet. Homozygotes: PCSK9 inhibitor, *lomitapide*, statin, *ezetimibe*; Heterozygotes: PCSK9 inhibitor, *bempedoic acid*, statin, *ezetimibe*. Other options: *cholestyramine*, *niacin*



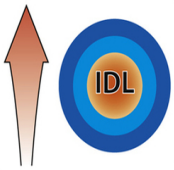
Type IIB (FAMILIAL COMBINED [MIXED] HYPERLIPIDEMIA)

- Similar to Type IIA except that VLDL is also increased, resulting in elevated serum TG as well as cholesterol levels.
- Caused by overproduction of VLDL by the liver.
- Relatively common.
- Treatment: Diet. Drug therapy is similar to that for Type IIA.



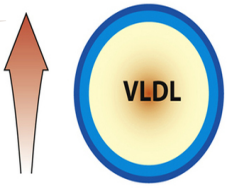
Type III (FAMILIAL DYSBETALIPOPROTEINEMIA)

- Serum concentrations of IDL are increased, resulting in increased TG and cholesterol levels.
- Cause is either overproduction or underutilization of IDL due to mutant apolipoprotein E.
- Xanthomas and accelerated vascular disease develop in patients by middle age.
- Treatment: Diet. Drug therapy includes *fenofibrate*, *icosapent ethyl*, or *niacin*. Statin for patients in statin benefit group.



Type IV (FAMILIAL HYPERTRIGLYCERIDEMIA)

- VLDL levels are increased, whereas LDL levels are normal or decreased, resulting in normal to elevated cholesterol and greatly elevated circulating TG levels.
- Cause is overproduction and/or decreased removal of VLDL and TG in serum.
- This is a relatively common disease. It has few clinical manifestations other than accelerated ischemic heart disease. Patients with this disorder are frequently obese, diabetic, and hyperuricemic.
- Treatment: Diet. If necessary, drug therapy includes *fenofibrate*, *icosapent ethyl*, or *niacin*. Statin for patients in statin benefit group.



Type V (FAMILIAL MIXED HYPERTRIGLYCERIDEMIA)

- Serum VLDL and chylomicrons are elevated. LDL is normal or decreased. This results in elevated cholesterol and greatly elevated TG levels.
- Cause is either increased production or decreased clearance of VLDL and chylomicrons. Usually, it is a genetic defect.

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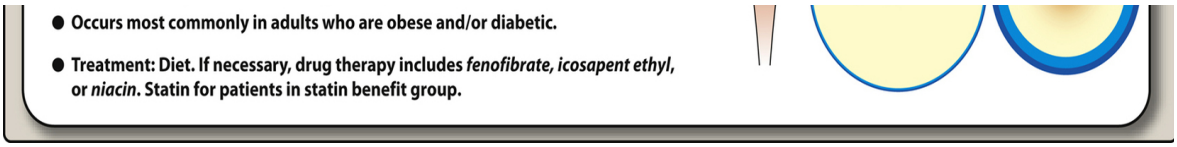

Figure 14.2 **A.** Normal metabolism of plasma lipoproteins. Roman numerals in the white circles refer to specific types of familial hyperlipidemias summarized on the facing page. **B.** Fredrickson classification of familial hyperlipidemias. apo CII = apolipoprotein CII found in chylomicrons and VLDL; CM = chylomicron; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; PCSK9 = proprotein convertase subtilisin kexin type 9; TG = triglyceride; VLDL = very-low-density lipoprotein.

II. TREATMENT GOALS

Plasma lipids consist mostly of lipoproteins, which are spherical complexes of lipids and specific proteins. The clinically important lipoproteins, listed in decreasing order of atherogenicity, are LDL-C, very-low-density lipoprotein (VLDL) and chylomicrons, and HDL. [Note: VLDL is a carrier for triglycerides. VLDL is not directly measured in the blood but is estimated by dividing the triglyceride value by 5 (for example, a triglyceride value of 150 mg/dL correlates to a VLDL of 30).] The occurrence of CHD is positively associated with high total cholesterol and has an even stronger correlation with elevated LDL-C. In contrast to LDL-C, high levels of HDL-C have been associated with a decreased risk for CHD (Figure 14.3). According to cholesterol guidelines, the need for antihyperlipidemic drug therapy should be determined based on an assessment of risk for ASCVD, in conjunction with evaluation of lipoprotein levels .

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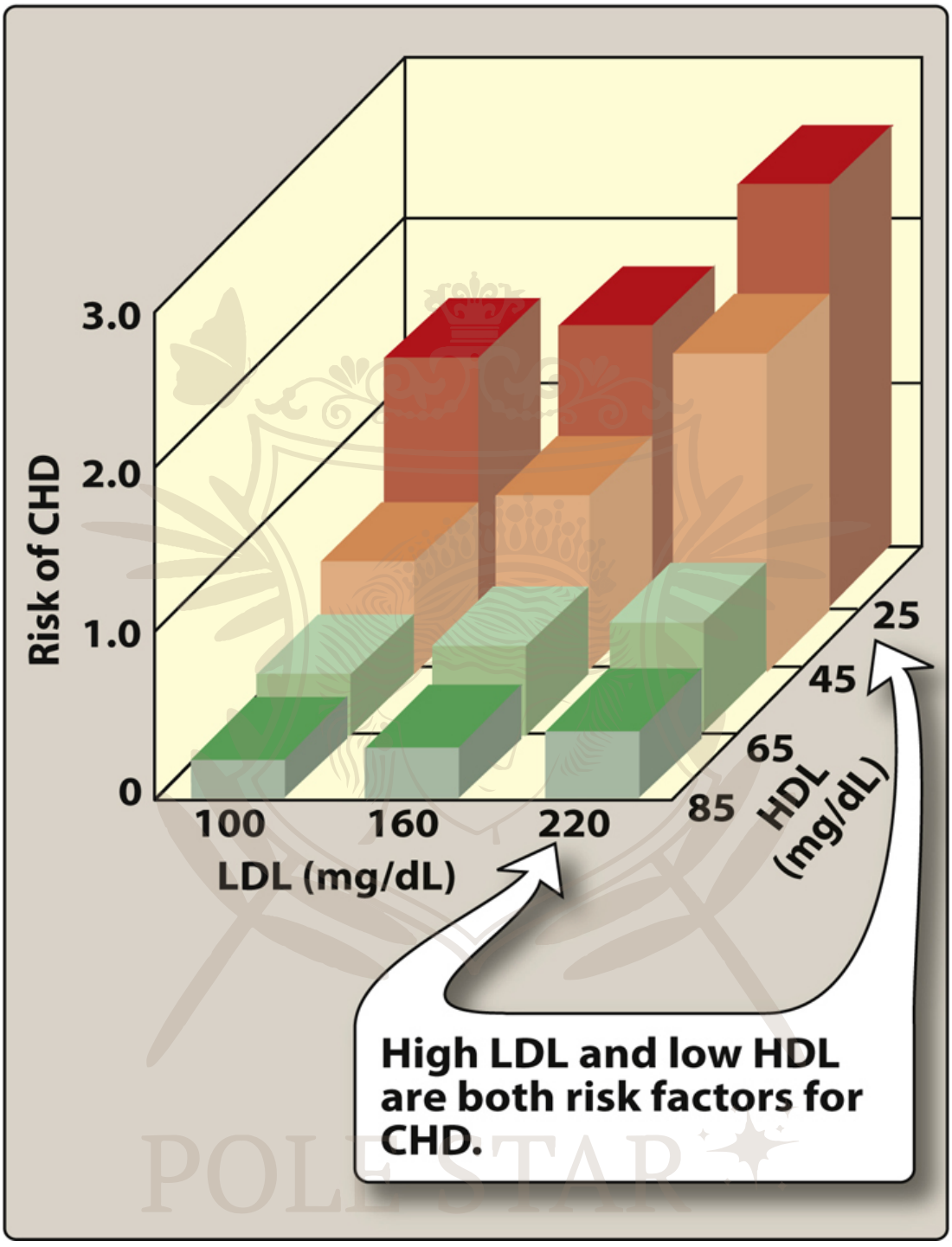

Figure 14.3 Effect of circulating low-density lipoprotein (LDL) and high-density lipoprotein (HDL) on the risk of coronary heart disease (CHD).

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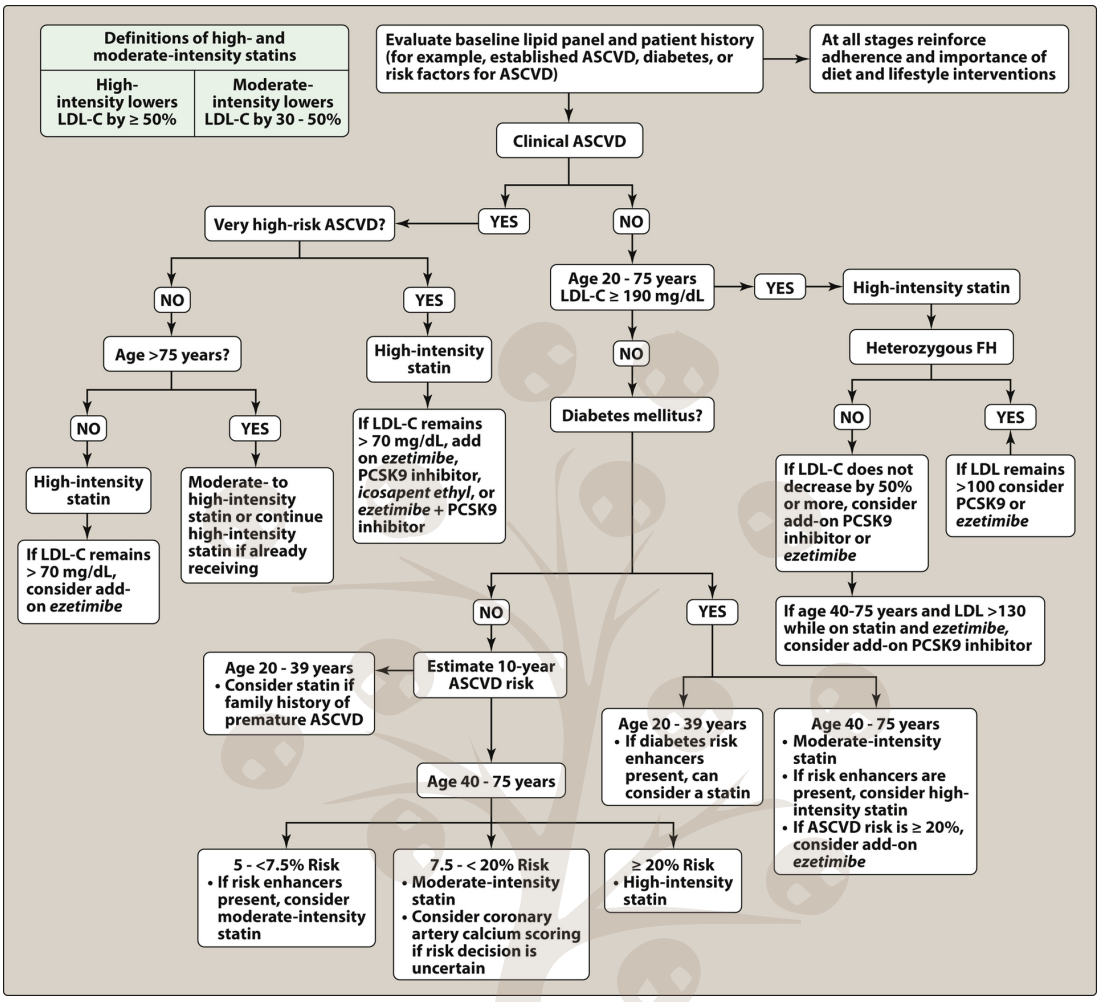

Figure 14.4 Treatment guidelines for hyperlipidemia.ASCVD = atherosclerotic cardiovascular disease; FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin kexin type 9; TG = triglycerides.

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III. DRUGS FOR HYPERLIPIDEMIA

Antihyperlipidemic drugs include agents that primarily target LDL-C (the statins, a cholesterol absorption inhibitor, bile acid sequestrants, proprotein convertase subtilisin kexin type 9 inhibitors, adenosine triphosphate-citrate lyase inhibitors, and microsomal triglyceride transfer protein inhibitors), as well as agents that target triglycerides (fibrates, *niacin*, and omega-3 fatty acids). Drug therapy for hyperlipidemia should

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always be accompanied by lifestyle modifications, such as exercise and a diet low in saturated fats.

A. HMG CoA reductase inhibitors

3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (commonly known as statins) lower LDL-C, resulting in a substantial reduction in coronary events and death from CHD. They are first-line treatment to reduce the occurrence of ASCVD events in high-risk patients (Figure 14.4). Therapeutic lifestyle changes, such as diet, exercise, and weight loss, may help reduce cholesterol levels; however, lifestyle modifications do not replace the need for drug therapy in patients who fall into one of the four statin benefit groups as outlined in Figure 14.4. [Note: The four statin benefit groups include patients with (1) clinical ASCVD, (2) LDL-C ≥ 190 mg/dL, (3) diabetes and age 40-75 years, or (4) elevated 10-year ASCVD risk and age 40-75 years.]

1.Mechanism of action: *Lovastatin* [LOE-vah-stat-in], *simvastatin* [sim-vah-STAT-in], *pravastatin* [PRAH-vah-stat-in], *atorvastatin* [a-TOR-vah-stat-in], *fluvastatin* [FLOO-vah-stat-in], *pitavastatin* [pit-AV-a-STAT-in], and *rosuvastatin* [roe-SOO-vah-stat-in] are competitive inhibitors of HMG CoA reductase, the rate-limiting step in cholesterol synthesis. By inhibiting de novo cholesterol synthesis, they deplete the intracellular supply of cholesterol (Figure 14.5). Depletion of intracellular cholesterol causes the cell to increase the number of cell surface LDL receptors that can bind and internalize circulating LDL-C. Thus, plasma cholesterol is reduced, by both decreased cholesterol synthesis and increased LDL-C catabolism. *Rosuvastatin* and *atorvastatin* are the most potent LDL-C lowering statins, followed by *pitavastatin*, *simvastatin*, *lovastatin*, *pravastatin*, and *fluvastatin.* [Note: Because these agents undergo a marked first-pass extraction by the liver, their dominant effect is on that organ.] The HMG CoA reductase inhibitors also decrease triglyceride levels and may increase HDL-C in some patients. Clinical benefits extend beyond the primary mechanism of cholesterol lowering and include pleiotropic effects, such as improved endothelial function, increased nitric oxide bioavailability, antioxidant properties,

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inhibition of inflammatory responses, and stabilization of atherosclerotic plaques.

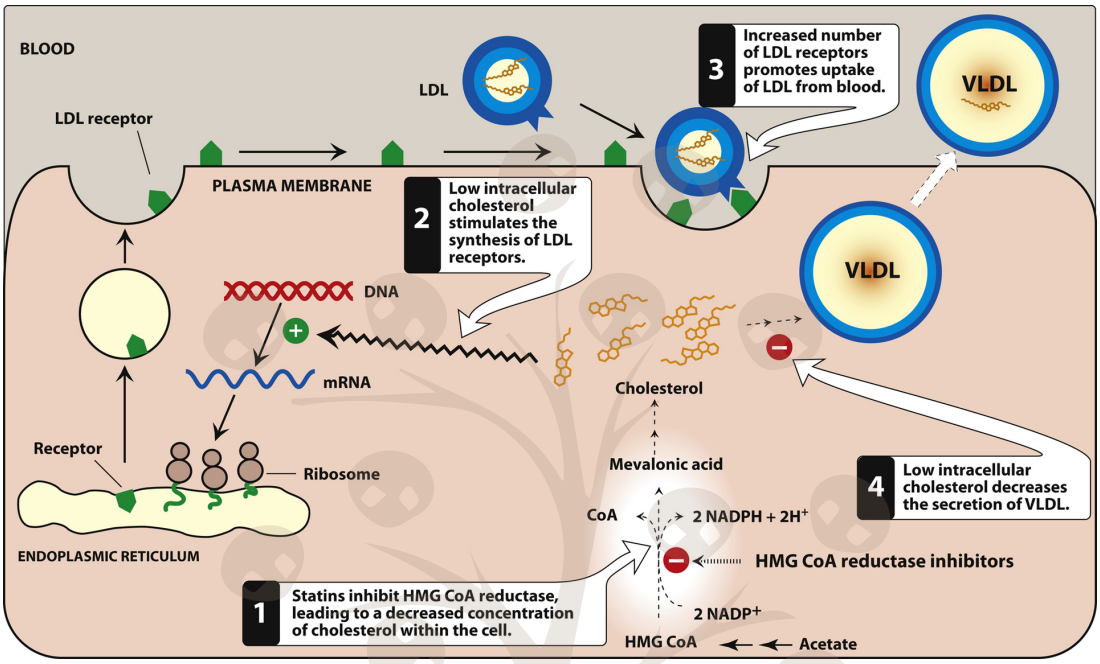

Figure 14.5 Inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase by the statin drugs.LDL = low-density lipoprotein; VLDL = very-low-density lipoprotein.

2.Therapeutic uses: These drugs are used to lower the risk of ASCVD events for patients in the four statin benefit groups. The intensity of statin therapy should be guided by the patient's absolute risk for an ASCVD event (Figure 14.4). [Note: *Rosuvastatin* and *atorvastatin* are the only statins that can provide high-intensity LDL-lowering effects.] Statins are effective in lowering plasma cholesterol levels in all types of hyperlipidemias. However, patients who have homozygous familial hypercholesterolemia (type IIA) and lack functional LDL receptors benefit much less from treatment with these drugs.

3.Pharmacokinetics: *Lovastatin* and *simvastatin* are lactones that are hydrolyzed to the active drug. The remaining statins are all administered in their active form. Absorption of the statins is

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variable (30%-85%) following oral administration. All statins are metabolized by cytochrome P450 (CYP) isoenzymes in the liver, except *pravastatin.* Excretion takes place principally through bile and feces, but some urinary elimination also occurs. Some characteristics of the statins are summarized in Figure 14.6.

Characteristic	*Atorvastatin*	*Fluvastatin*	*Lovastatin*	*Pitavastatin*	*Pravastatin*	*Rosuvastatin*	*Simvastatin*
Serum LDL cholesterol reduction produced (%)	55	24	34	43	34	60	41
Serum triglyceride reduction produced (%)	29	10	16	18	24	18	18
Serum HDL cholesterol increase produced (%)	6	8	9	8	12	8	12
Plasma half-life (h)	14	2–3	2	12	1–2	19	1–2
Penetration of central nervous system	No	No	Yes	Yes	No	No	Yes
Renal excretion of absorbed dose (%)	2	< 6	10	15	20	10	13

Figure 14.6 Summary of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors.HDL = high-density lipoprotein; LDL = low-density lipoprotein.

4.Adverse effects: Elevated liver enzymes may occur with statin therapy. Therefore, liver function should be evaluated prior to starting therapy or if a patient develops symptoms consistent with liver dysfunction while receiving a statin. [Note: Hepatic insufficiency can cause drug accumulation.] Myalgia (muscle pain, aches, or cramps), myopathy, and rhabdomyolysis (breakdown of muscle tissue leading to release of myoglobin in blood; rare) have been reported (Figure 14.7). Risk factors for rhabdomyolysis include frailty or low body mass, hypertension, renal insufficiency, vitamin D deficiency, hypothyroidism, advanced age, female sex, alcohol or drug abuse, and use of drugs that increase the risk of muscle adverse effects, such as macrolide antibiotics (*clarithromycin*, *erythromycin*), *daptomycin*, *itraconazole*, *cyclosporine*, *gemfibrozil*, *colchicine*, some protease inhibitors, and grapefruit juice. *Simvastatin*, *lovastatin*, and *atorvastatin* are major substrates of CYP3A4, and inhibitors of this enzyme may increase

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the risk of rhabdomyolysis. Plasma creatine kinase levels should be measured in patients with muscle complaints. The HMG CoA reductase inhibitors may also increase the effect of *warfarin.* Thus, it is important to evaluate the international normalized ratio (INR) when initiating a statin or changing the dosage. These drugs are contraindicated during pregnancy, lactation, and active liver disease.

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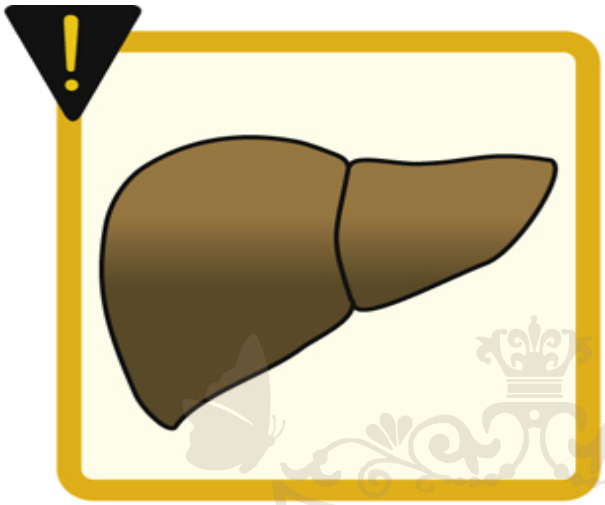
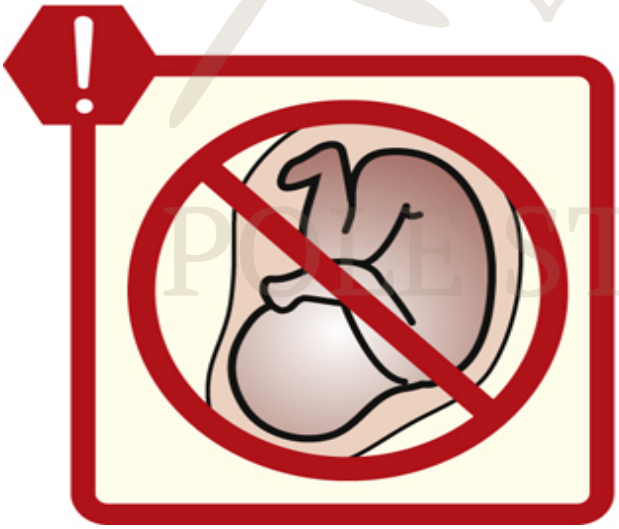


Liver dysfunction

Myopathy



Contraindicated in pregnancy

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Figure 14.7 Some adverse effects and precautions associated with 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors.

B. Cholesterol absorption inhibitor

Ezetimibe [eh-ZEH-teh-mibe] selectively inhibits absorption of dietary and biliary cholesterol in the small intestine, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood. *Ezetimibe* lowers LDL-C by approximately 18% to 23%. Due its modest LDL-C lowering, *ezetimibe* is often used as an adjunct to maximally tolerated statin therapy in patients with high ASCVD risk or in statin-intolerant patients. *Ezetimibe* is primarily metabolized in the small intestine and liver via glucuronide conjugation, with subsequent biliary and renal excretion. Patients with moderate to severe hepatic insufficiency should not be treated with *ezetimibe.* Adverse effects are uncommon with the use of *ezetimibe*.

C. Bile acid sequestrants

Bile acid sequestrants (resins) have modest LDL-C lowering effects, and the benefits are less than those observed with statins.

1.Mechanism of action: *Cholestyramine resin* [koe-LES-tir-a-meen], *colestipol* [koe-LES-tih-pole], and *colesevelam* [koh-le-SEV-e-lam] are anion-exchange resins that bind negatively charged bile acids and bile salts in the small intestine (Figure 14.8). The resin/bile acid complex is excreted in the feces, thus lowering the bile acid concentration. This causes hepatocytes to increase conversion of cholesterol to bile acids, which are essential components of the bile. Consequently, intracellular cholesterol concentrations decrease, which activates an increased hepatic uptake of cholesterol-containing LDL-C particles, leading to a decrease in plasma LDL-C. [Note: This increased uptake is mediated by an upregulation of cell surface LDL receptors.]

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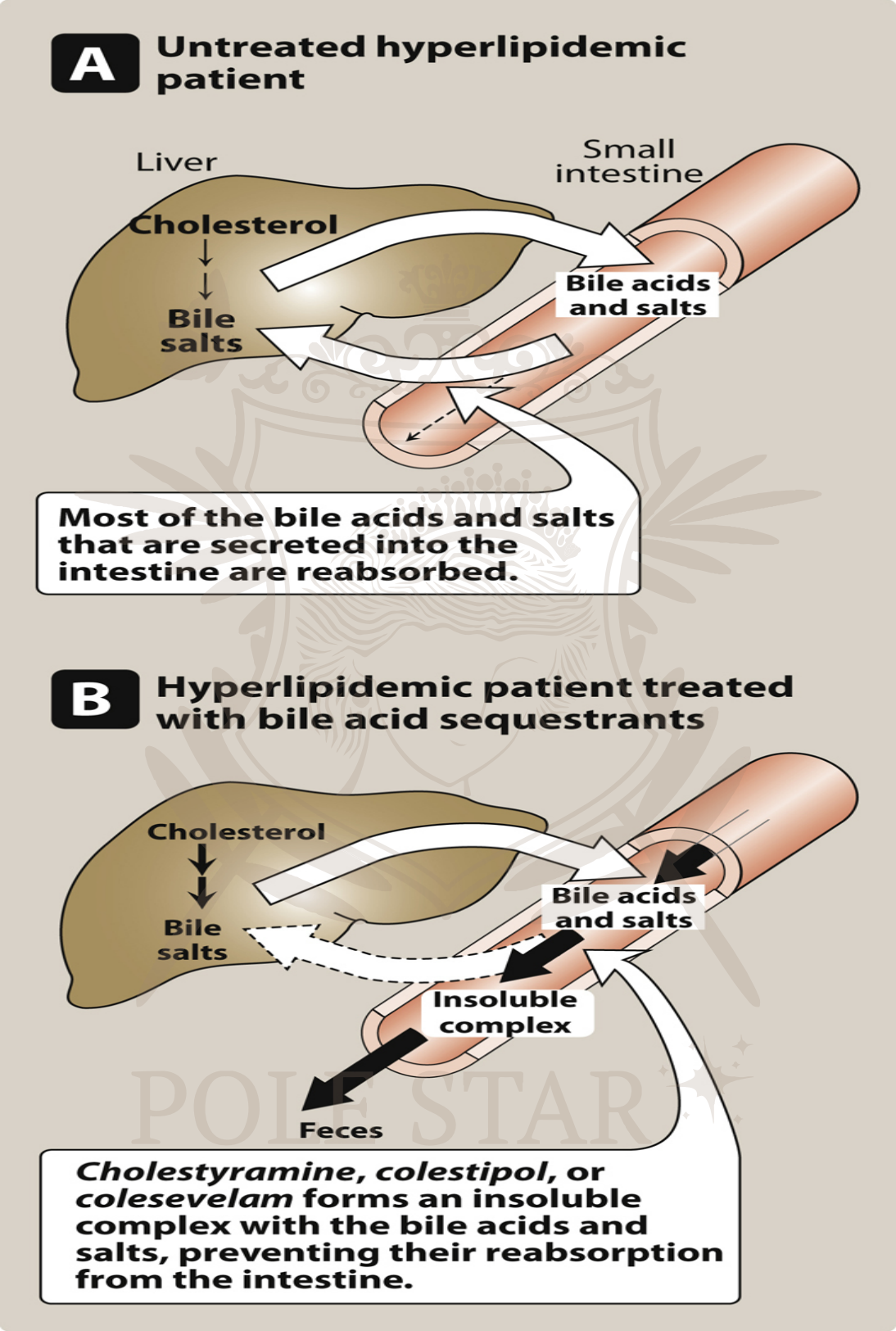

Figure 14.8 Mechanism of bile acid sequestrants.

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2.Therapeutic uses: The bile acid sequestrants may be useful (often in combination with diet or other medications) for treating type IIA and type IIB hyperlipidemias. Due to a lack of evidence demonstrating a reduction in the risk for ASCVD events, as well as poor tolerability, the bile acid sequestrants are often reserved for patients who cannot tolerate other lipid lowering therapies. [Note: In those rare individuals who are homozygous for type IIA in which functional LDL receptors are essentially undetectable, these drugs have little effect on plasma LDL-C levels.] *Cholestyramine* can also relieve pruritus caused by accumulation of bile acids in patients with biliary stasis. *Colesevelam* is also indicated for type 2 diabetes due to its glucose-lowering effects. [Note: These agents are available as a powder for solution or as a tablet. The powder formulation may be objectionable to patients due to the sandy or gritty texture, and the pill burden with the tablets is high (requiring up to 16 tablets per day). This limits the clinical use of these agents.]

3.Pharmacokinetics: Bile acid sequestrants are insoluble in water and have large molecular weights. After oral administration, they are neither absorbed nor metabolically altered by the intestine. Instead, they are totally excreted in feces.

4.Adverse effects: The most common adverse effects are gastrointestinal (GI) disturbances, such as constipation, nausea, and flatulence. *Colesevelam* has fewer GI side effects than other bile acid sequestrants. These agents may impair the absorption of the fat-soluble vitamins (A, D, E, and K), and they interfere with the absorption of many drugs (for example, *digoxin*, *warfarin*, and thyroid hormone). Therefore, other drugs should be taken at least 1 to 2 hours before, or 4 to 6 hours after, the bile acid sequestrants. These agents may raise triglyceride levels and are contraindicated in patients with significant hypertriglyceridemia (greater than 400 mg/dL). They should be used with caution in patients with gastroparesis or other significant GI motility disorders.

D. Proprotein convertase subtilisin kexin type 9 inhibitors

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Proprotein convertase subtilisin kexin type 9 (PCSK9) is an enzyme predominantly produced in the liver. PCSK9 binds to the LDL receptor on the surface of hepatocytes, leading to the degradation of LDL receptors (Figure 14.9). By inhibiting the PCSK9 enzyme, more LDL receptors are available to clear LDL-C from the serum. *Alirocumab* [al-i-ROK-ue-mab] and *evolocumab* [e-voe-LOK-ue-mab] are PCSK9 inhibitors, which are fully humanized monoclonal antibodies. These agents are used in addition to maximally tolerated statin therapy in patients with heterozygous or homozygous familial hypercholesterolemia or in patients with clinical ASCVD who require additional LDL-C lowering. When combined with statin therapy, PCSK9 inhibitors provide potent LDL-C lowering (50%-70%). They may also be considered for patients with high ASCVD risk and statin intolerance. PCSK9 inhibitors are available as subcutaneous injections and are administered every 2 to 4 weeks. PCSK9 inhibitors are generally well tolerated. The most common adverse drug reactions are injection site reactions, immunologic or allergic reactions, nasopharyngitis, diarrhea, myalgia, and upper respiratory tract infections.

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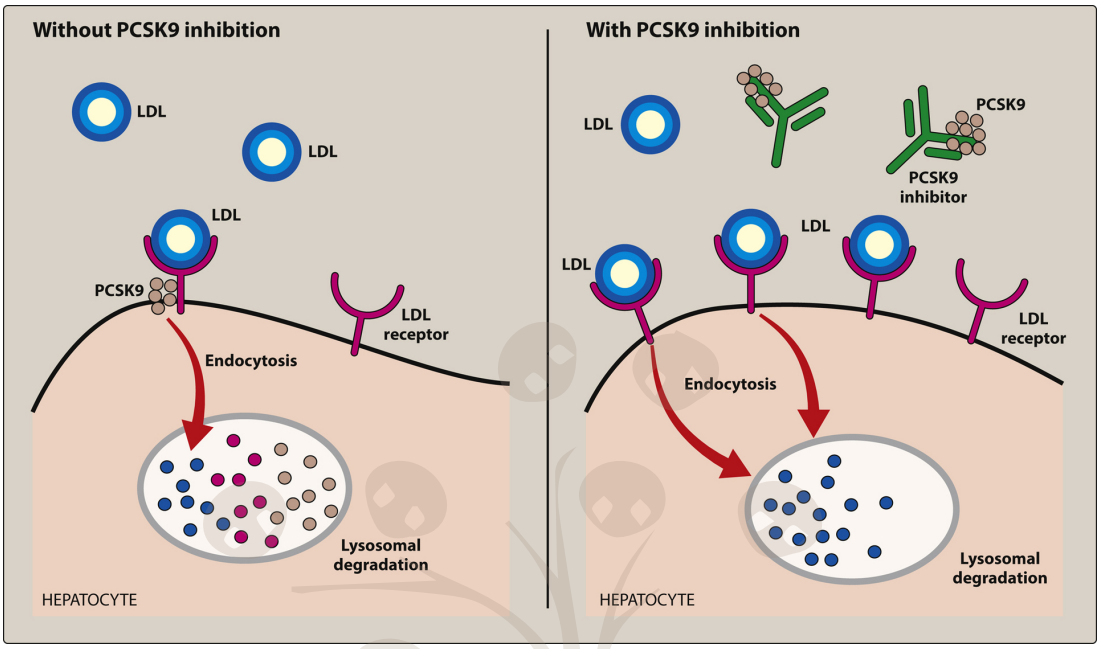

Figure 14.9 Mechanism of action of PCSK9 inhibitors.PCSK9 binds to the LDL receptor on the surface of hepatocytes, leading to degradation of LDL receptors. Inhibition of PCSK9 prevents degradation of LDL receptors and promotes greater clearance of LDL-C from the serum. LDL = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin kexin type 9.

E. Adenosine triphosphate-citrate lyase inhibitor

Bempedoic (BEM-pe-DOE-ik) *acid* is an adenosine triphosphate-citrate lyase (ACL) inhibitor that lowers LDL-C by inhibiting cholesterol synthesis in the liver with a target, ACL, which is further upstream from HMG CoA reductase. This agent is used in addition to maximally tolerated statin therapy in patients with heterozygous familial hypercholesterolemia or in patients with ASCVD who require additional LDL-C lowering. *Bempedoic acid* reduces LDL-C by an additional 12% to 17% when added on to other therapies. Administered orally as a prodrug, it is metabolized in the liver to the active form and secreted primarily in the urine as the glucuronide metabolite. Overall, it is well tolerated; however, hyperuricemia has been reported, and it must be used with caution in patients with a history of gout. Other adverse reactions may include limb or back pain, muscle spasm, or tendon rupture.

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Clinical Application 14.1: Considerations for Use of HMG CoA Reductase Inhibitors

An HMG CoA reductase inhibitor ("statin") should be initiated to reduce the risk of ASCVD events for patients who fall into one of the four statin benefit groups. For patients who do not have ASCVD, diabetes, or extremely elevated LDL-C, an estimation of ASCVD risk may be performed to determine if the patient is a candidate for statin therapy (for example, patients 40-75 years of age with an ASCVD risk score of 7.5% or higher). The ASCVD risk reflects the 10-year risk of an ASCVD event, and it may be estimated using a standardized risk estimator (for example, https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/). When selecting statin therapy, the intensity of therapy (for example, high intensity or moderate intensity) is determined by the risk of ASCVD events, as outlined in the treatment algorithm (Figure 14.4). Only higher doses of *atorvastatin* and *rosuvastatin* are considered high-intensity statin therapy (lowers LDL-C by 50% or more), while lower doses of these two agents and most other statins are capable of achieving moderate-intensity therapy (lowers LDL-C by 30%-50%). Possible adverse effects and prescribing precautions need to be taken into consideration. For example, patients should be followed for the development of liver dysfunction and myopathies while on statin therapy. Patients should be evaluated for the risk of complications before starting therapy and educated on possible adverse reactions.

F. Microsomal triglyceride transfer protein inhibitor

Lomitapide (loe-MI-ta-pide) is indicated for homozygous familial hypercholesterolemia (HoFH), which is often ineffectively treated by HMG CoA reductase inhibitors. As a microsomal triglyceride transfer protein inhibitor, its unique mechanism of action leads to a reduction in VLDL release and VLDL-mediated triglyceride secretion. This leads to a reduction in LDL concentrations by up to 51%. *Lomitapide* is prescribed as an adjunct to other lipid lowering therapies and optimized lifestyle in HoFH. Due to the potential for hepatotoxicity, this agent is part of a risk evaluation and mitigation strategy drug safety program, which mandates regular monitoring of liver function. Other possible adverse reactions include chest pain, fatigue, GI distress (diarrhea, nausea, vomiting, dyspepsia), infection, and respiratory issues (nasopharyngitis, nasal congestion). Drug interactions must be considered since it is a substrate and inhibitor of CYP3A4 metabolism. Coadministration with moderate to strong inhibitors of CYP3A4 is contraindicated.

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G. Fibrates

Fenofibrate [fen-oh-FIH-brate] and *gemfibrozil* [jem-FI-broh-zill] are derivatives of fibric acid that lower serum triglycerides and increase HDL-C.

1.Mechanism of action: The peroxisome proliferator–activated receptors (PPARs) are members of the nuclear receptor family that regulate lipid metabolism. PPARs function as ligand-activated transcription factors. Upon binding to their natural ligands (fatty acids or eicosanoids) or antihyperlipidemic drugs (*fenofibrate* or *gemfibrozil*), PPARs are activated. Following activation, they bind to peroxisome proliferator response elements, which ultimately leads to decreased triglyceride concentrations through increased expression of lipoprotein lipase (Figure 14.10) and a decreased apolipoprotein (apo) CIII concentration. *Fenofibrate* is more effective than *gemfibrozil* in lowering triglyceride levels. Fibrates also increase HDL-C by increasing the expression of apo AI and apo AII.

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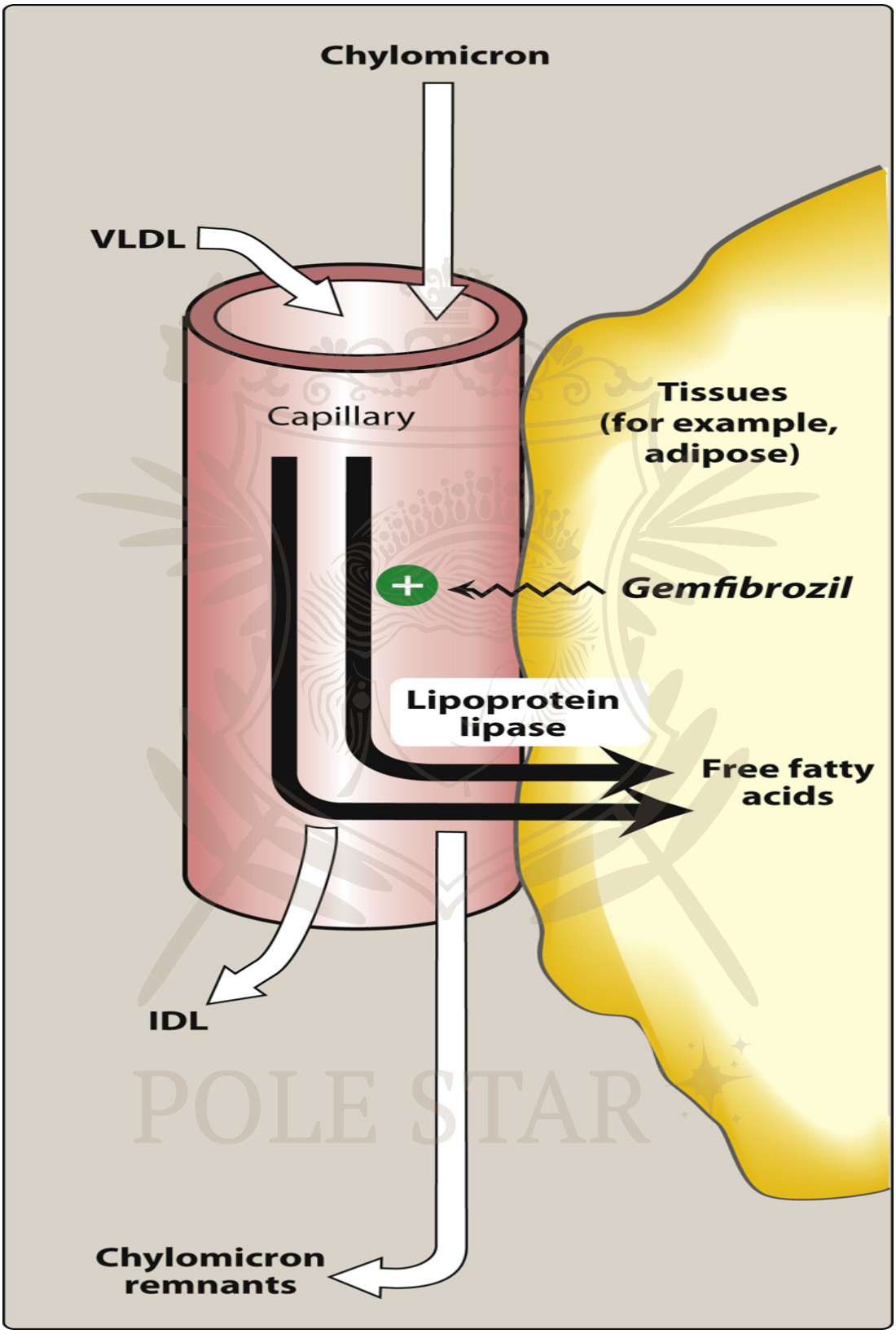

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Figure 14.10 Activation of lipoprotein lipase by *gemfibrozil*.IDL = intermediate-density lipoprotein; VLDL = very-low-density lipoprotein.

2.Therapeutic uses: The fibrates are used in the treatment of hypertriglyceridemia. They are particularly useful in treating type III hyperlipidemia (dysbetalipoproteinemia), in which intermediate-density lipoprotein particles accumulate. Fibrates are not indicated for cardiovascular benefits or reduction of ASCVD events. However, guidelines support their use in severe hypertriglyceridemia, which could lead to pancreatitis.

3.Pharmacokinetics: *Gemfibrozil* and *fenofibrate* are completely absorbed after oral administration and distribute widely, bound to albumin. *Fenofibrate* is a prodrug, which is converted to the active moiety, fenofibric acid. Both drugs undergo extensive biotransformation and are excreted in the urine as glucuronide conjugates.

4.Adverse effects: The most common adverse effects are mild GI disturbances. These lessen as the therapy progresses. Because these drugs increase biliary cholesterol excretion, there is a predisposition to form gallstones. Myositis (muscle inflammation) can occur with fibrates, and muscle weakness or tenderness should be evaluated. Patients with renal insufficiency may be at higher risk of myositis. Myopathy and rhabdomyolysis have been reported in patients taking *gemfibrozil* and statins together. The use of *gemfibrozil* is contraindicated with *simvastatin*, and, in general, the use of *gemfibrozil* with any statin should be avoided. Both fibrates may increase the effects of *warfarin.* Therefore, INR should be monitored more frequently when a fibrate is initiated. Fibrates should not be used in patients with severe hepatic or renal dysfunction, preexisting gallbladder disease, or biliary cirrhosis. They should be used with caution in pregnancy.

H. Niacin (nicotinic acid)

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Niacin [NYE-uh-sin] reduces triglycerides by 20% to 50%. It also reduces LDL-C by 10% to 20% and is the most effective agent for increasing HDL-C. *Niacin* can be used in combination with statins. [Note: The addition of *niacin* to statin therapy has not been shown to provide any additional reduction in the risk of ASCVD events or mortality.]

1.Mechanism of action: *Niacin* strongly inhibits lipolysis in adipose tissue, thereby reducing production of free fatty acids (Figure 14.11). The liver normally uses circulating free fatty acids as a major precursor for triglyceride synthesis. Reduced liver triglyceride levels decrease hepatic VLDL production, which in turn reduces LDL-C plasma concentrations.

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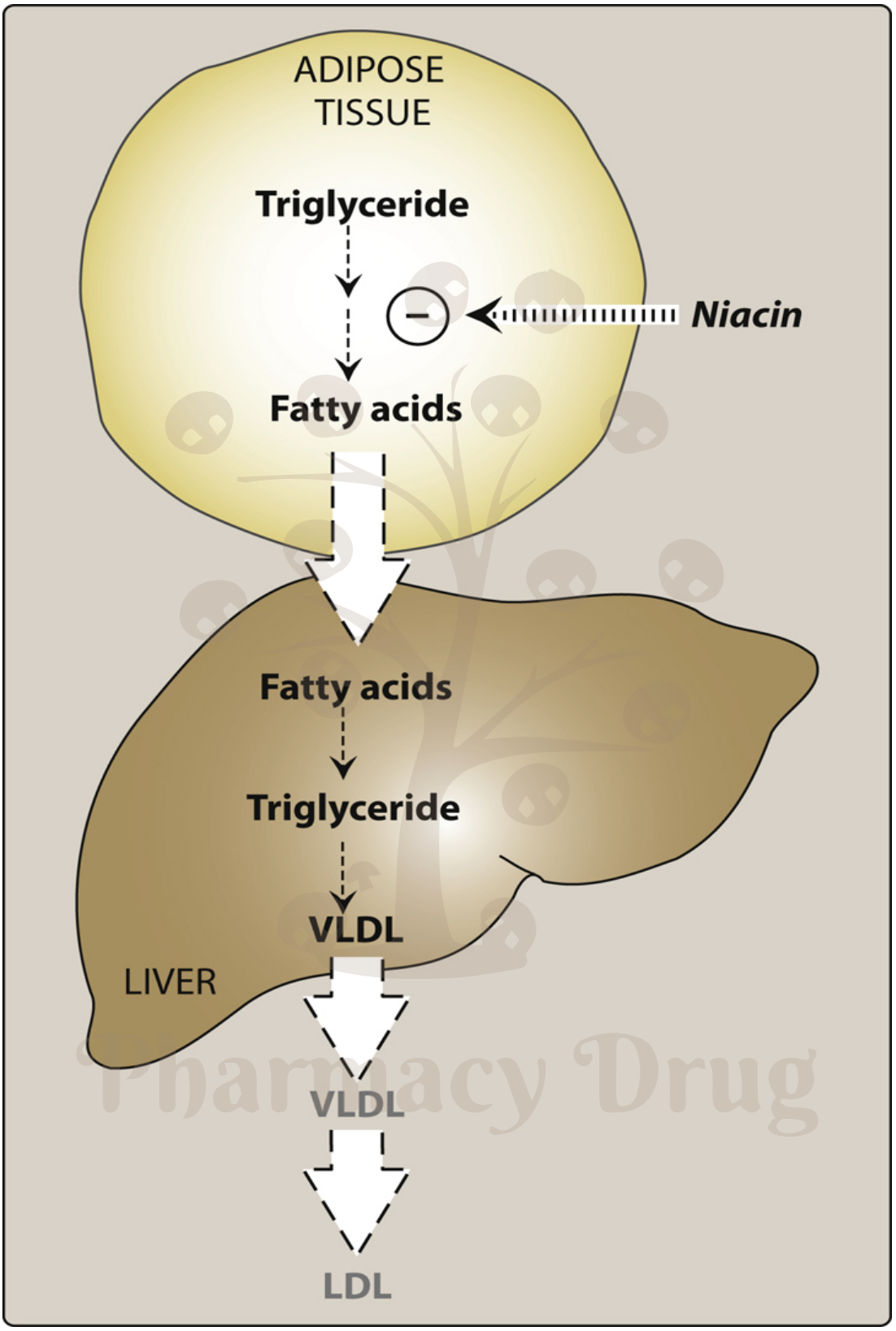

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Figure 14.11 *Niacin* inhibits lipolysis in adipose tissue, resulting in decreased hepatic very-low-density lipoprotein (VLDL) synthesis and production of low-density lipoprotein (LDL) in the plasma.

2.Therapeutic uses: *Niacin* has limited indications. Unlike the statins, *niacin* is not indicated for cardiovascular benefits or reduction of ASCVD events. Since it lowers plasma levels of both cholesterol and triglycerides, *niacin* may be used in the treatment of familial hyperlipidemias or in patients intolerant to HMG CoA reductase inhibitors.

3.Pharmacokinetics: *Niacin* is administered orally. It is converted in the body to nicotinamide, which is incorporated into the cofactor nicotinamide adenine dinucleotide (NAD^+). *Niacin*, its nicotinamide derivative, and other metabolites are excreted in the urine. [Note: Administration of nicotinamide alone does not decrease plasma lipid levels.]

4.Adverse effects: The most common adverse effects of *niacin* are an intense cutaneous flush accompanied by an uncomfortable feeling of warmth and pruritus. Administration of *aspirin* 30 minutes prior to taking *niacin* decreases the flush, which is prostaglandin mediated. Some patients also experience nausea and abdominal pain with *niacin.* Slow titration of the dose or use of the sustained-release formulation of *niacin* reduces bothersome initial adverse effects. *Niacin* inhibits tubular secretion of uric acid and predisposes patients to hyperuricemia and gout. Impaired glucose tolerance and hepatotoxicity have also been reported. The drug should be avoided in active hepatic disease or in patients with an active peptic ulcer.

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I. Omega-3 fatty acids

Omega-3 polyunsaturated fatty acids (PUFAs) are essential fatty acids that are predominantly used for triglyceride lowering. Essential fatty acids inhibit VLDL and triglyceride synthesis in the liver. The omega-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found in marine sources such as tuna, halibut, and salmon. Approximately 4 g of marine-derived omega-3 PUFAs daily decreases

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serum triglyceride concentrations by 25% to 30%, with small increases in LDL-C and HDL-C. Over-the-counter or prescription fish oil capsules (EPA/DHA) can be used for supplementation, as it is difficult to consume enough omega-3 PUFAs from dietary sources alone. *Icosapent* [eye-KOE-sa-pent] *ethyl* is a prescription product that contains only EPA and, unlike other fish oil supplements, does not significantly raise LDL-C. Omega-3 PUFAs can be considered as an adjunct to other lipid-lowering therapies for individuals with elevated triglycerides (≥500 mg/dL). Although effective for triglyceride lowering, in general, omega-3 PUFA supplementation has not been shown to reduce cardiovascular morbidity and mortality. An exception is *icosapent ethyl*, which has been shown to reduce the risk of cardiovascular events in secondary prevention patients or high-risk primary prevention patients when added to a statin. The most common side effects of omega-3 PUFAs include GI effects (abdominal pain, nausea, diarrhea) and a fishy aftertaste. Bleeding risk can be increased in those who are concomitantly taking anticoagulants or antiplatelet agents.

J. Combination drug therapy

It is sometimes necessary to use more than one antihyperlipidemic drug to achieve treatment goals. Patients with established ASCVD or an elevated 10-year risk of ASCVD or those who do not achieve intended LDL-C reductions on maximally tolerated statin therapy may be considered for combination therapy. *Ezetimibe*, PCSK9 inhibitors, and *icosapent ethyl* can be considered for add-on therapy, since there is evidence that these combinations further reduce ASCVD events in patients already taking statin therapy. Combination drug therapy is not without risks. Liver and muscle toxicities occur more frequently with lipid-lowering drug combinations. Figure 14.12 summarizes some actions of the antihyperlipidemic drugs.

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TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIGLYCERIDES
HMG CoA reductase inhibitors (statins)	↓↓↓↓	↑↑	↓↓
Cholesterol absorption inhibitor	↓	↑	↓
Bile acid sequestrants	↓↓↓	↑	↑
PCSK9 inhibitors	↓↓↓↓↓	↑↑	↓
ACL inhibitor	↓↓	—	—
MTP inhibitor	↓↓↓↓	—	↓↓
Fibrates	↓	↑↑↑	↓↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓↓
Omega-3 fatty acids			
EPA+DHA	↑↑	—	↓↓↓↓
EPA	—	—	↓↓

Figure 14.12 Characteristics of antihyperlipidemic drug families.ACL = adenosine triphosphate-citrate lyase; HDL = high-density lipoprotein; HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LDL = low-density lipoprotein; MTP = microsomal triglyceride transfer protein; PCSK9 = proprotein convertase subtilisin kexin type 9.

Clinical Application 14.2: Maintenance of Target Cholesterol Levels

Combination therapy may be needed in numerous populations unable to maintain target cholesterol levels despite maximized therapy with HMG CoA reductase inhibitors (statins) and an optimized diet. Only *ezetimibe,* PCSK9 inhibitors, and *icosapent ethyl* have evidence that these combinations further reduce ASCVD events in patients already taking statin therapy. *Bempedoic acid* does not have outcome data supporting cardiovascular benefit at this time. *Lomitapide* has a unique indication (HoFH) in which first-line HMG CoA reductase therapy has been shown to be ineffective. Agents such as *niacin*, fibrates, or bile acid sequestrants may rarely be used in combination to achieve target cholesterol levels, but due to limited cardiovascular benefit and/or drug–drug interactions and poor tolerability, these agents are usually reserved only for patients who are unable to tolerate other options.

Chapter Summary

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- Coronary heart disease is the leading cause of death worldwide and has been correlated with dyslipidemia. Drug therapy used in conjunction with lifestyle changes, such as a low-fat diet and exercise, have demonstrated a significant reduction in CHD mortality.
- The primary goal of treatment for hyperlipidemia is to reduce the risk of future ASCVD events. A secondary goal is to maintain lower optimized levels for LDL-C and triglycerides and appropriate levels of HDL-C.
- Antihyperlipidemic drugs include the statins, cholesterol absorption inhibitors, bile acid sequestrants, proprotein convertase subtilisin kexin type 9 inhibitors, adenosine triphosphate-citrate lyase (ACL) inhibitors, microsomal triglyceride transfer protein inhibitors, fibrates, *niacin,* and omega-3 fatty acids.
- 3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, "statins," such as *simvastatin*, *pravastatin*, *atorvastatin,* and *rosuvastatin,* are considered first-line treatment for patients with elevated risk of ASCVD. These agents help reduce the occurrence (or recurrence) of ASCVD events, with benefits extending beyond reduction of cholesterol levels, including atherosclerotic plaque stabilization, improvement of coronary endothelial function, inhibition of platelet thrombus formation, and vascular anti-inflammatory activity.
- Combination therapy may be necessary to obtain optimal control of LDL-C. *Ezetimibe,* PCSK9 inhibitors, and/or *icosapent ethyl* can be considered for add-on therapy, since there is evidence that these combinations further reduce ASCVD events in patients already taking statin therapy.
- The ACL inhibitor, *bempedoic acid*, is approved for use in combination with maximally tolerated HMG CoA reductase inhibitors, although its effect on cardiovascular mortality has not been established.
- *Lomitapide* is a microsomal triglyceride transfer protein inhibitor indicated for homozygous familial hypercholesterolemia.
- Fibrates, *niacin*, and omega-3 fatty acids are used for the management of elevated triglycerides.

STUDY QUESTIONS

Choose the ONE best answer.

14.1 A 19-year-old man is diagnosed with type 1 hyperlipidemia characterized by elevated plasma levels of chylomicrons. Which of the following treatment options would be most appropriate to address the dyslipidemia?

A. Ezetimibe
B. Simvastatin

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C. PCSK9 inhibitor
D. Dietary adjustments to include a low-fat diet

Correct answer = D. Type I hyperlipidemia (hyperchylomicronemia) is treated with a low-fat diet (making D correct). No drug therapy is effective for this disorder.

14.2 Which of the following drugs decreases cholesterol synthesis by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase?

A. Fenofibrate
B. Colestipol
C. Rosuvastatin
D. Gemfibrozil

Correct answer = C. Rosuvastatin decreases cholesterol synthesis by inhibiting HMG CoA reductase. Fenofibrate and gemfibrozil increase the activity of lipoprotein lipase, thereby increasing the removal of VLDL from plasma. Colestipol lowers the amount of bile acids returning to the liver via the enterohepatic circulation.

14.3 A 47-year-old man with a history of renal insufficiency, gout, atrial fibrillation, and hypertriglyceridemia is being started on an HMG CoA reductase inhibitor. Which risk factor will most likely increase the possibility of myalgia or myopathy with the new medication?

A. Renal insufficiency
B. Gout
C. Hypertriglyceridemia
D. Atrial fibrillation

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Correct answer = A. Patients with a history of renal insufficiency have a higher incidence of developing myalgias, myopathy, and rhabdomyolysis with use of HMG CoA reductase inhibitors (statins), especially with those that are renally eliminated as drug accumulation can occur. The other populations have not been reported to have a higher incidence of this adverse effect with HMG CoA reductase inhibitors.

14.4 A 47-year-old woman presents to her family medicine physician for her annual exam. She has a past medical history of

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hypertension, obesity, and tobacco use (20 pack-year history). A fasting lipid panel reveals an LDL of 125 mg/dL, and her estimated ASCVD risk is calculated to be 10%. Which of the following best characterizes the statin benefit group for this patient?

A. Group 1—history of clinical ASCVD
B. Group 3—Age 40 to 75 years with diabetes
C. Group 4—Age 40 to 75 years without diabetes and ASCVD risk >7.5%
D. Does not fit into any statin benefit group

Correct answer = C. Choice A is incorrect as she has no history of clinical ASCVD events. Choice B is incorrect as she does not have a history of diabetes. Choice D is incorrect as she is greater than 40 years of age and has a calculated ASCVD risk of 10%, which puts her into statin benefit group 4 (making choice C correct).

14.5 A 63-year-old woman with elevated LDL-C levels is unable to tolerate statins due to adverse effects, including severe muscle pain. The physician would like to prescribe a non-statin drug to effectively lower her LDL-C levels. What medication would be the most effective treatment?

A. Niacin
B. Alirocumab
C. Cholestyramine
D. Ezetimibe

Correct answer = B. Alirocumab is a PCSK9 inhibitor that can lower LDL-C by approximately 50%. Niacin primarily raises HDL-C and decreases triglycerides, with less potent effects on LDL-C lowering. Cholestyramine and ezetimibe both lower LDL-C, although not as potently as PCSK9 inhibitors.

14.6 Which of the following drugs binds bile acids in the intestine, thus preventing their return to the liver via the enterohepatic circulation?

A. Niacin
B. Gemfibrozil
C. Cholestyramine

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D. Simvastatin

Correct answer = C. Cholestyramine is an anion-exchange resin that binds negatively charged bile acids and bile salts in the small intestine. The resin/bile acid complex is excreted in the feces, thus preventing the bile acids from returning to the liver by the enterohepatic circulation. The other choices do not bind intestinal bile acids.

14.7 A 65-year-old man presents to his physician for the management of type 2 diabetes mellitus and an elevated LDL-C of 165 mg/dL. Which of the following is the best option to lower the LDL-C levels and decrease the risk of ASCVD events in this patient?

A. Bempedoic acid
B. Colesevelam
C. Atorvastatin
D. Fenofibrate

Correct answer = C. Atorvastatin, an HMG CoA reductase inhibitor (statin), is the most effective option for lowering LDL-C, achieving reductions of up to 60% from baseline levels. Statins are the primary modality for reducing ASCVD risk when drug therapy is indicated. Bempedoic acid lowers LDL-C modestly compared with the LDL-C reduction achieved by statins. Colesevelam can reduce LDL-C, but not as effectively as statins. While colesevelam has glucose-lowering effects, those effects are modest, and it is not a preferred agent for type 2 diabetes. Fenofibrate is more effective at lowering triglyceride levels or raising HDL-C.

14.8 A 42-year-old man was started on sustained-release niacin 2 weeks ago. He reports uncomfortable flushing and itchiness that he thinks is related to the niacin. Which of the following can help manage these adverse effects?

A. Administer aspirin 30 minutes prior to taking niacin.
B. Administer aspirin 30 minutes after taking niacin.
C. Increase the dose of niacin.
D. Change the sustained-release niacin to immediate-release niacin.

Correct answer = A. Flushing associated with niacin is prostaglandin mediated; therefore, use of aspirin (a prostaglandin inhibitor) can help to minimize this adverse

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effect. It must be administered 30 minutes before the dose of the niacin; therefore, choice B is incorrect. Increasing the dose of niacin is likely to increase these complaints; therefore, choice C is incorrect. The sustained-release formulation of niacin has less incidence of flushing versus that of the immediate release; therefore, choice D is incorrect.

14.9 A 55-year-old woman presents to her primary care physician for her annual exam. Her past medical history includes prediabetes, hypertension, and obesity. Her estimated ASCVD risk is calculated at 6.5%, and her fasting lipid panel reveals hypertriglyceridemia (triglycerides 655 mg/dL). Which of the following treatments would be most important to start immediately?

A. Ezetimibe
B. Simvastatin
C. Icosapent ethyl
D. Alirocumab

Correct answer = C. Due to the ASCVD risk of 6.5%, lipid-lowering therapy is not definitively needed to reduce the risk for ASCVD events, as the risk does not exceed 7.5% (making choice B incorrect). A is incorrect as ezetimibe monotherapy would not be indicated in patients who have not failed statin therapy. Choice D is incorrect as alirocumab would be reserved for patients failing statin therapy or those with significant elevations in LDL and to lower the risk of ASCVD events (which this patient is at low risk for). Choice C is correct as she is experiencing severe hypertriglyceridemia and is at risk for pancreatitis; fish oils can significantly lower triglycerides and of the available options have the greatest effect on triglycerides.

14.10 A 62-year-old man is being discharged from the hospital today after suffering a myocardial infarction. Which of the following is the most appropriate intensity of statin therapy for this patient?

A. Low-intensity statin
B. Moderate-intensity statin
C. High-intensity statin
D. Statin not indicated

Correct answer = C. The patient has a recent history of an ASCVD event (myocardial infarction). Patients with clinical ASCVD should receive a high-intensity statin due to their elevated risk for recurrent ASCVD events. Choices A and B would only be indicated if the patient was unable to tolerate a higher statin intensity. Choice D is

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incorrect as a statin is indicated for this patient given the clinical ASCVD event he suffered.

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Unit IV:
Drugs Affecting the Central Nervous System

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15

Drugs for Neurodegenerative Diseases

Jose A. Rey

I. OVERVIEW

Most drugs that affect the central nervous system (CNS) act by altering some step in the neurotransmission process. Drugs affecting the CNS may act presynaptically by influencing the production, storage, release, or termination of action of neurotransmitters. Other agents may activate or block postsynaptic receptors. This chapter provides an overview of the CNS, with a focus on those neurotransmitters that are involved in the actions of many clinically useful CNS drugs. These concepts are useful in understanding the etiology and treatment strategies of neurodegenerative disorders that respond to drug therapy, including Parkinson disease (PD) and Alzheimer disease (AD; Figure 15.1), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS).

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DRUGS FOR PARKINSON DISEASE

Amantadine GOCOVRI
Apomorphine APOKYN, KYNMOBI
Benztropine COGENTIN
Bromocriptine PARLODEL
Carbidopa LODOSYN
Entacapone COMTAN
Levodopa (w/ Carbidopa) SINEMET
Levodopa (w/ Carbidopa+ Entacapone) STALEVO
Istradefylline NOURIANZ
Opicapone ONGENTYS
Pramipexole MIRAPEX
Rasagiline AZILECT
Ropinirole REQUIP
Rotigotine NEUPRO
Safinamide XADAGO
Selegiline (Deprenyl) ELDEPRYL, ZELAPAR
Tolcapone TASMAR
Trihexyphenidyl GENERIC ONLY

DRUGS FOR ALZHEIMER DISEASE

Aducanumab ADUHELM
Donepezil ARICEPT
Galantamine RAZADYNE
Memantine NAMENDA
Rivastigmine EXELON

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Figure 15.1 Summary of agents used in the treatment of Parkinson disease and Alzheimer disease.

II. NEUROTRANSMISSION IN THE CNS

The basic functioning of neurons in the CNS is similar to that of the autonomic nervous system (ANS) described in Chapter 3. For example, transmission of information in both the CNS and in the periphery involves the release of neurotransmitters that diffuse across the synaptic cleft to bind to specific receptors on the postsynaptic neuron. In both systems, the recognition of the neurotransmitter by the membrane receptor of the postsynaptic neuron triggers intracellular changes. However, several major differences exist between neurons in the peripheral ANS and those in the CNS. The circuitry of the CNS is more complex than that of the ANS, and the number of synapses in the CNS is far greater. The CNS, unlike the peripheral ANS, contains networks of inhibitory neurons that are constantly active in modulating the rate of neuronal transmission. In addition, the CNS communicates through the use of multiple neurotransmitters, whereas the ANS uses only two primary neurotransmitters, acetylcholine and norepinephrine.

III. SYNAPTIC POTENTIALS

In the CNS, receptors in most synapses are coupled to ion channels. Binding of the neurotransmitter to the postsynaptic membrane receptors results in a rapid but transient opening of ion channels. Open channels allow specific ions inside and outside the cell membrane to flow down their concentration gradients. The resulting change in the ionic composition across the membrane of the neuron alters the postsynaptic potential, producing either depolarization or

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hyperpolarization of the postsynaptic membrane, depending on the specific ions and the direction of their movement.

A. Excitatory pathways

Neurotransmitters can be classified as either excitatory or inhibitory, depending on the nature of the action they elicit. Stimulation of excitatory neurons causes a movement of ions that results in a depolarization of the postsynaptic membrane. These excitatory postsynaptic potentials (EPSP) are generated by the following: (1) Stimulation of an excitatory neuron causes the release of neurotransmitters, such as glutamate or acetylcholine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of sodium (Na^+) ions. (2) The influx of Na^+ causes a weak depolarization, or EPSP, that moves the postsynaptic potential toward its firing threshold. (3) If the number of stimulated excitatory neurons increases, more excitatory neurotransmitter is released. This ultimately causes the EPSP depolarization of the postsynaptic cell to pass a threshold, thereby generating an all-or-none action potential. [Note: The generation of a nerve impulse typically reflects the activation of synaptic receptors by thousands of excitatory neurotransmitter molecules released from many nerve fibers.] Figure 15.2 shows an example of an excitatory pathway.

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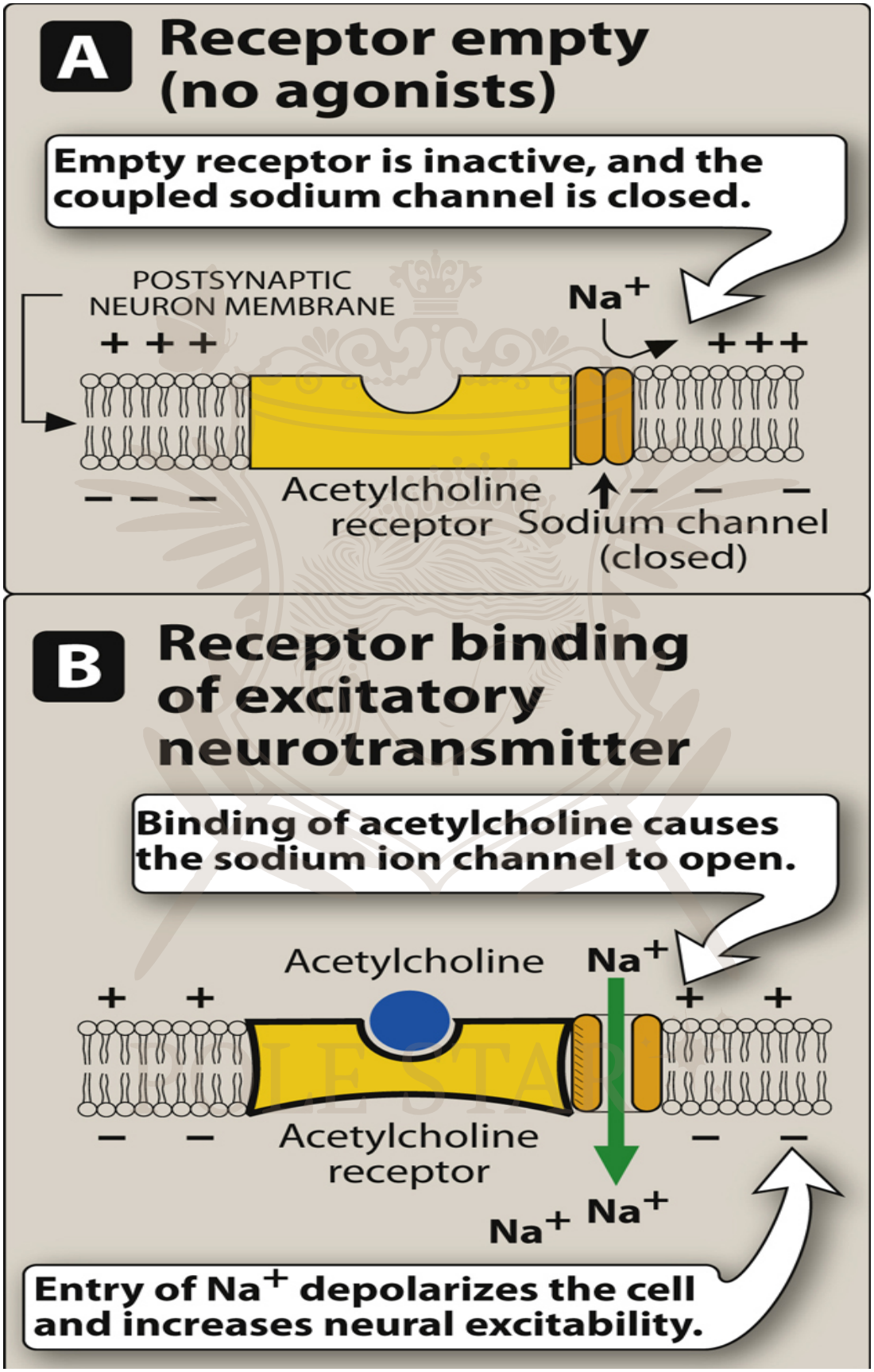
A
Receptor empty (no agonists)
Empty receptor is inactive, and the coupled sodium channel is closed.
POSTSYNAPTIC NEURON MEMBRANE
Na+
+ + +
+++
– – –
Acetylcholine receptor
Sodium channel (closed)
B
Receptor binding of excitatory neurotransmitter
Binding of acetylcholine causes the sodium ion channel to open.
Acetylcholine
Na+
+ +
+ +
– –
– –
Acetylcholine receptor
Na+
Na+
Entry of Na+ depolarizes the cell and increases neural excitability.

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Figure 15.2 Binding of the excitatory neurotransmitter, acetylcholine, causes depolarization of the neuron.

B. Inhibitory pathways

Stimulation of inhibitory neurons causes movement of ions that results in a hyperpolarization of the postsynaptic membrane. These inhibitory postsynaptic potentials (IPSP) are generated by the following: (1) Stimulation of inhibitory neurons releases neurotransmitters, such as γ-aminobutyric acid (GABA) or glycine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of specific ions, such as potassium (K^+) and chloride (Cl^-). (2) The influx of Cl^- and efflux of K^+ cause a weak hyperpolarization, or IPSP, that moves the postsynaptic potential away from its firing threshold. This diminishes the generation of action potentials. Figure 15.3 shows an example of an inhibitory pathway.

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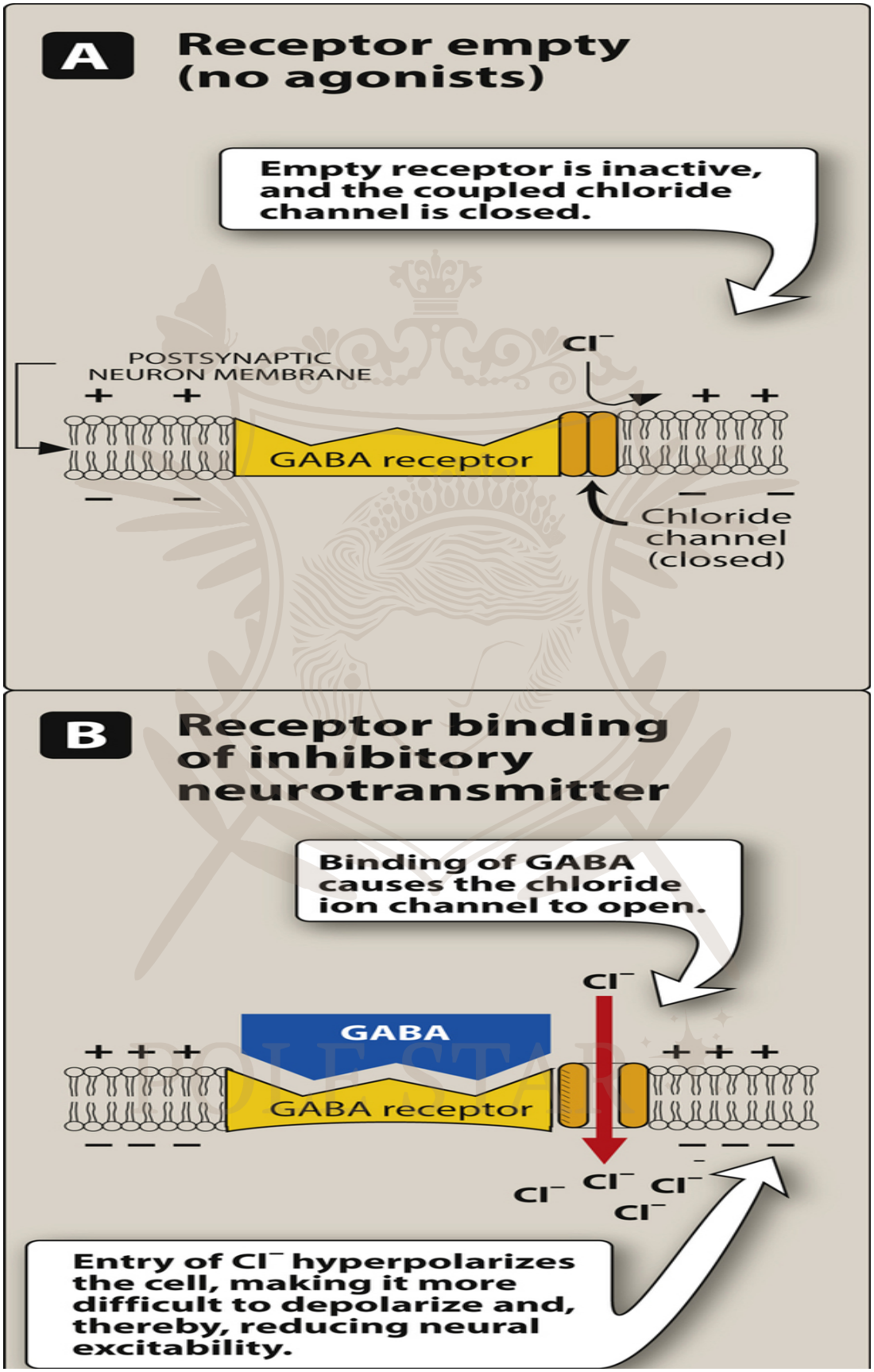
A
Receptor empty (no agonists)
Empty receptor is inactive, and the coupled chloride channel is closed.
POSTSYNAPTIC NEURON MEMBRANE
Cl⁻
GABA receptor
Chloride channel (closed)
B
Receptor binding of inhibitory neurotransmitter
Binding of GABA causes the chloride ion channel to open.
Cl⁻
GABA
GABA receptor
Cl⁻ Cl⁻ Cl⁻ Cl⁻
Entry of Cl⁻ hyperpolarizes the cell, making it more difficult to depolarize and, thereby, reducing neural excitability.

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Figure 15.3 Binding of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA), causes hyperpolarization of the neuron.

C. Combined effects of the EPSP and IPSP

Most neurons in the CNS receive both EPSP and IPSP input. Thus, several different types of neurotransmitters may act on the same neuron, but each binds to its own specific receptor. The overall action is the summation of the individual actions of the various neurotransmitters on the neuron. The neurotransmitters are not uniformly distributed in the CNS but are localized in specific clusters of neurons, the axons of which may synapse with specific regions of the brain. Many neuronal tracts, thus, seem to be chemically coded, and this may offer greater opportunity for selective pharmacological modulation of certain neuronal pathways.

IV. NEURODEGENERATIVE DISEASES

Neurodegenerative diseases of the CNS include PD, AD, MS, and ALS. These devastating illnesses are characterized by the progressive loss of selected neurons in discrete areas of the brain, resulting in characteristic disorders of movement, cognition, or both.

V. OVERVIEW OF PARKINSON DISEASE

Parkinsonism is a progressive neurological disorder of muscle movement, characterized by tremors, muscular rigidity, bradykinesia, and postural and gait abnormalities. Most cases involve people over the age of 65 years.

A. Etiology

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The cause of PD is unknown for most patients. The disease is correlated with destruction of dopaminergic neurons in the substantia nigra with a consequent reduction of dopamine actions in the striatum, a cluster of neurons in the basal ganglia that are involved in motor control.

1.Substantia nigra: The substantia nigra, part of the extrapyramidal system, is the source of dopaminergic neurons (Figure 15.4) that terminate in the neostriatum. Each dopaminergic neuron makes thousands of synaptic contacts within the neostriatum and therefore modulates the activity of a large number of cells. These dopaminergic projections from the substantia nigra fire tonically rather than in response to specific muscular movements or sensory input. Thus, the dopaminergic system appears to serve as a sustained tonic influence on motor activity, rather than participating in specific movements.

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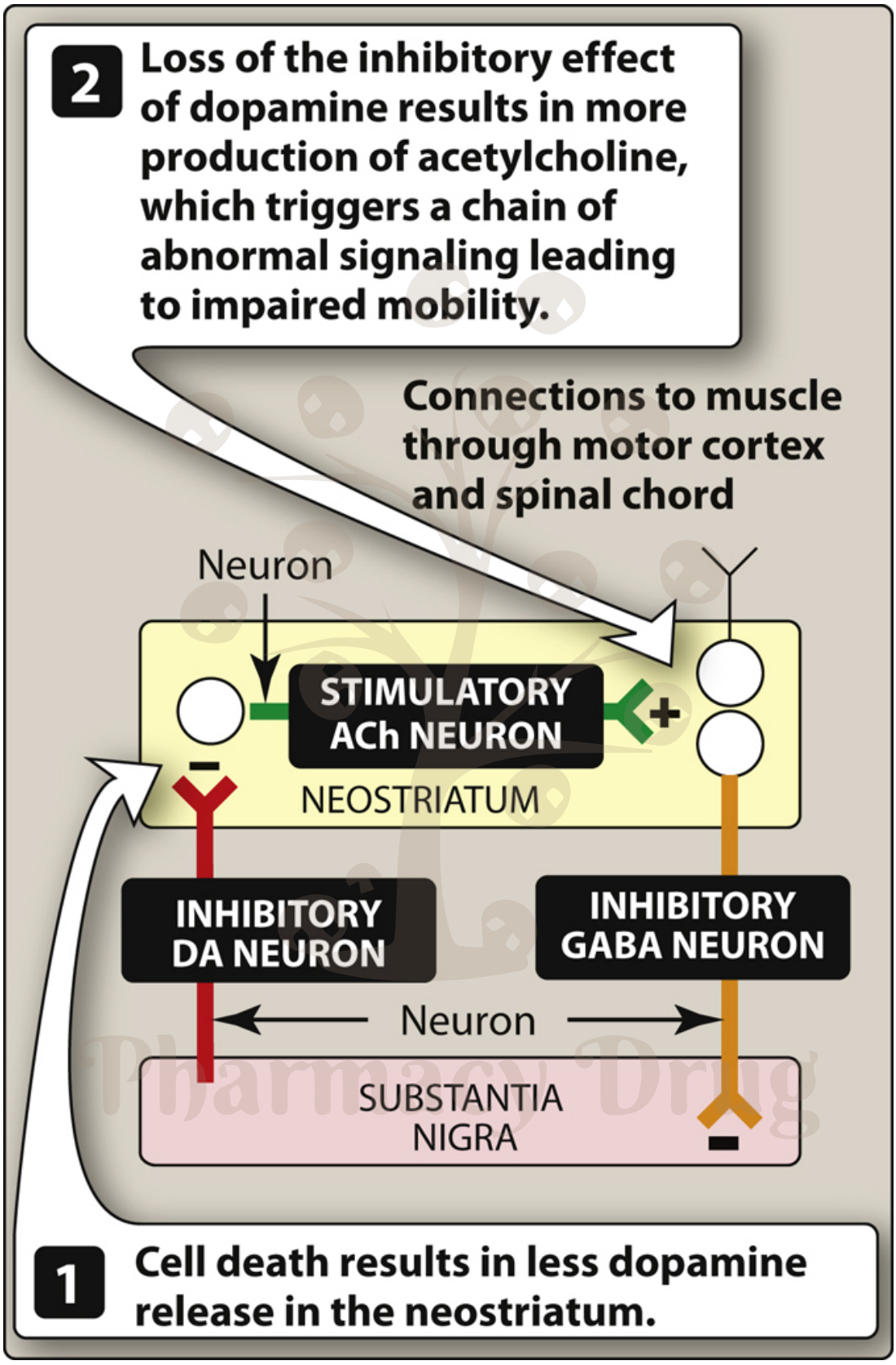

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Figure 15.4 Role of substantia nigra in Parkinson disease.ACh = acetylcholine; DA = dopamine; GABA = γ-aminobutyric acid.

2.Neostriatum: Normally, the neostriatum is connected to the substantia nigra by neurons (Figure 15.4) that secrete the inhibitory transmitter GABA at their termini. In turn, cells of the substantia nigra send neurons back to the neostriatum, secreting the inhibitory transmitter dopamine at their termini. This mutual inhibitory pathway normally maintains a degree of inhibition of both areas. In PD, destruction of cells in the substantia nigra results in the degeneration of the nerve terminals that secrete dopamine in the neostriatum. Thus, the normal inhibitory influence of dopamine on cholinergic neurons in the neostriatum is significantly diminished, resulting in overproduction, or a relative overactivity, of acetylcholine by the stimulatory neurons (Figure 15.4). This triggers a chain of abnormal signaling, resulting in loss of the control of muscle movements.

3.Secondary parkinsonism: Drugs such as the phenothiazines and *haloperidol*, whose major pharmacologic action is blockade of dopamine receptors in the brain, may produce parkinsonian symptoms (also called pseudoparkinsonism). These drugs should be used with extreme caution in patients with PD and in some cases are even contraindicated. All antipsychotics, or other agents that block dopamine receptors, are expected to have some degree of risk (low or high) for causing pseudoparkinsonism.

B. Strategy of treatment

In addition to an abundance of inhibitory dopaminergic neurons, the neostriatum is also rich in excitatory cholinergic neurons that oppose the action of dopamine (Figure 15.4). Many of the symptoms of parkinsonism reflect an imbalance between the excitatory cholinergic neurons and the greatly diminished number

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of inhibitory dopaminergic neurons. Therapy is aimed at restoring dopamine in the basal ganglia and antagonizing the excitatory effect of cholinergic neurons, thus reestablishing the correct dopamine/acetylcholine balance.

VI. DRUGS USED IN PARKINSON DISEASE

Many currently available drugs aim to maintain CNS dopamine levels, or signaling, as constant as possible. These agents only offer temporary relief from the symptoms of PD and do not arrest or reverse the neuronal degeneration caused by the disease.

A. Levodopa and carbidopa

Levodopa [lee-voe-DOE-pa] is a metabolic precursor of dopamine (Figure 15.5). It restores dopaminergic neurotransmission in the neostriatum by enhancing the synthesis of dopamine in the surviving neurons of the substantia nigra. In early disease, the number of residual dopaminergic neurons in the substantia nigra (typically about 20% of normal) is adequate for conversion of *levodopa* to dopamine. Thus, in new patients, the therapeutic response to *levodopa* is consistent, and the patient rarely complains that the drug effects “wear off.” Unfortunately, with time, the number of neurons decreases and fewer cells are capable of converting exogenously administered *levodopa* to dopamine. Consequently, motor control fluctuation develops. Relief provided by *levodopa* is only symptomatic, and it lasts only while the drug is present in the body.

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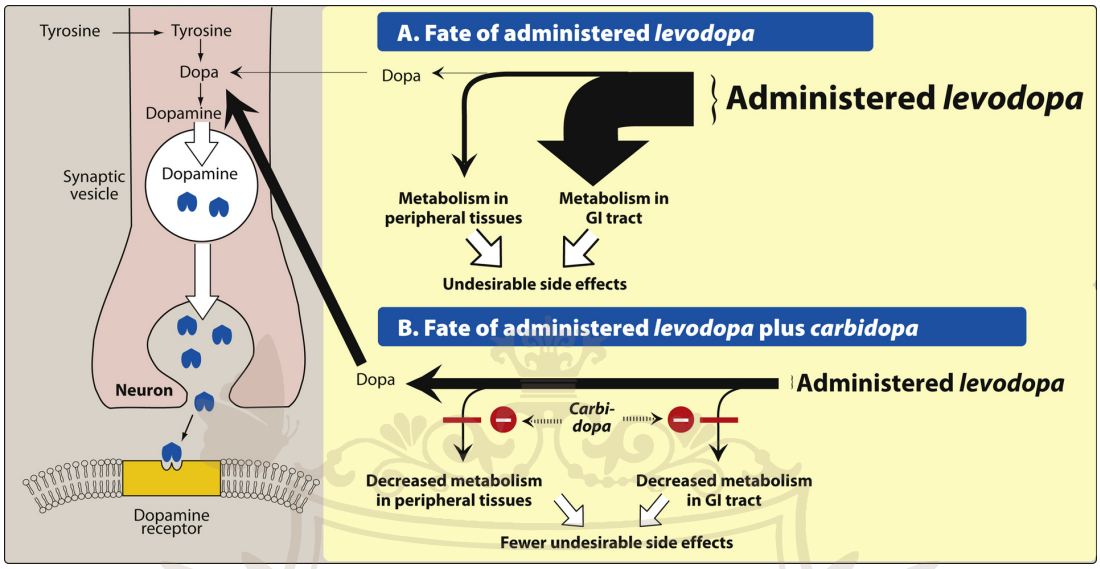

Figure 15.5 Synthesis of dopamine from *levodopa* in the absence and presence of *carbidopa*, an inhibitor of dopamine decarboxylase in the peripheral tissues.GI = gastrointestinal.

1.Mechanism of action

a. Levodopa: Dopamine does not cross the blood–brain barrier, but its immediate precursor, *levodopa*, is actively transported into the CNS and converted to dopamine (Figure 15.5). *Levodopa* must be administered with *carbidopa* [kar-bi-DOE-pa]. Without *carbidopa*, much of the drug is decarboxylated to dopamine in the periphery, resulting in diminished effect, nausea, vomiting, cardiac arrhythmias, and hypotension.

b. Carbidopa: *Carbidopa*, a dopamine decarboxylase inhibitor, diminishes the metabolism of *levodopa* in the periphery, thereby increasing the availability of *levodopa* to the CNS. The addition of *carbidopa* lowers the dose of *levodopa* needed by four- to fivefold and, consequently, decreases the severity of adverse effects arising from peripherally formed dopamine.

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2.Therapeutic uses: *Levodopa* in combination with *carbidopa* is an efficacious drug regimen for the treatment of PD and is often considered a first-line treatment. It is effective for the management of bradykinetic symptoms and can also decrease rigidity and tremors. In approximately two-thirds of patients with PD, *levodopa–carbidopa* substantially reduces the severity of symptoms for the first few years of treatment. Patients typically experience a decline in response during the 3rd to 5th year of therapy. Withdrawal from the drug must be gradual.

3.Absorption and metabolism: The drug is absorbed rapidly from the small intestine (when empty of food). *Levodopa* has an extremely short half-life (1-2 hours), which causes fluctuations in plasma concentration. This may produce fluctuations in motor response, which generally correlate with the plasma concentration of *levodopa*, or perhaps give rise to the more troublesome "on–off" phenomenon, in which the motor fluctuations are not related to plasma levels in a simple way. Motor fluctuations may cause the patient to suddenly lose normal mobility and experience tremors, cramps, and immobility. Ingestion of meals, particularly if high in protein, interferes with the absorption of *levodopa.* Thus, *levodopa* should be taken on an empty stomach, typically 30 minutes before a meal.

4.Adverse effects

a. Peripheral effects: Anorexia, nausea, and vomiting occur because of stimulation of the chemoreceptor trigger zone (Figure 15.6). Orthostatic hypotension is a common adverse effect, especially in early therapy. Tachycardia and ventricular extrasystole result from dopaminergic action on the heart, but these effects are less frequent. Patients with a history of cardiac disease should be carefully monitored for the possible development of arrhythmias. Adrenergic action on the iris causes mydriasis.

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In some individuals, blood dyscrasias and a positive reaction to the Coombs test are seen. Saliva and urine may appear dark because of the melanin pigment produced from catecholamine oxidation.

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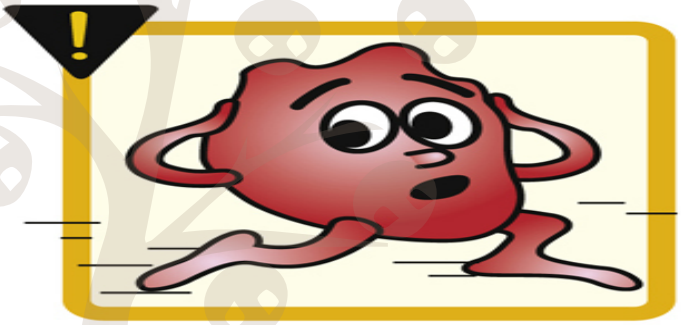
Anorexia

Nausea

Tachycardia



Hypotension

Psychiatric problems

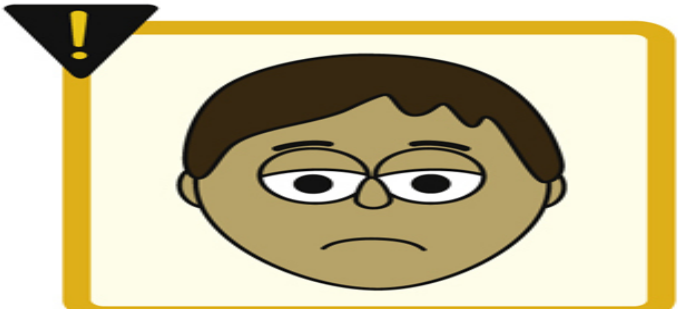


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Figure 15.6 Adverse effects of *levodopa*.

b. CNS effects: Visual and auditory hallucinations and abnormal involuntary movements (dyskinesias) may occur. These effects are the opposite of parkinsonian symptoms and reflect overactivity of dopamine in the basal ganglia. *Levodopa* can also cause somnolence, dizziness, mood changes, depression, psychosis, anxiety, and loss of impulse control. In patients with psychosis, *levodopa* may exacerbate symptoms, possibly through the buildup of central catecholamines.

Antipsychotic drugs are generally contraindicated in PD, because they potently block dopamine receptors and may augment parkinsonian symptoms. However, low doses of atypical antipsychotics, such as *quetiapine* or *clozapine*, are sometimes used to treat *levodopa*-induced psychosis. *Pimavanserin* [PIM-a-VAN-ser-in] is a serotonin (5-HT)2A receptor inverse agonist and antagonist that is approved for the management of PD psychosis. Given its lack of direct dopamine receptor antagonism, *pimavanserin* has a very low risk of causing extrapyramidal adverse effects and worsening the movement disorder.

5. Interactions: The vitamin pyridoxine (B_6) increases the peripheral breakdown of *levodopa* and diminishes its effectiveness (Figure 15.7). Concomitant administration of *levodopa* and nonselective monoamine oxidase inhibitors (MAOIs), such as *phenelzine*, can produce a hypertensive crisis caused by enhanced catecholamine production. Therefore, concomitant administration of these agents is contraindicated.

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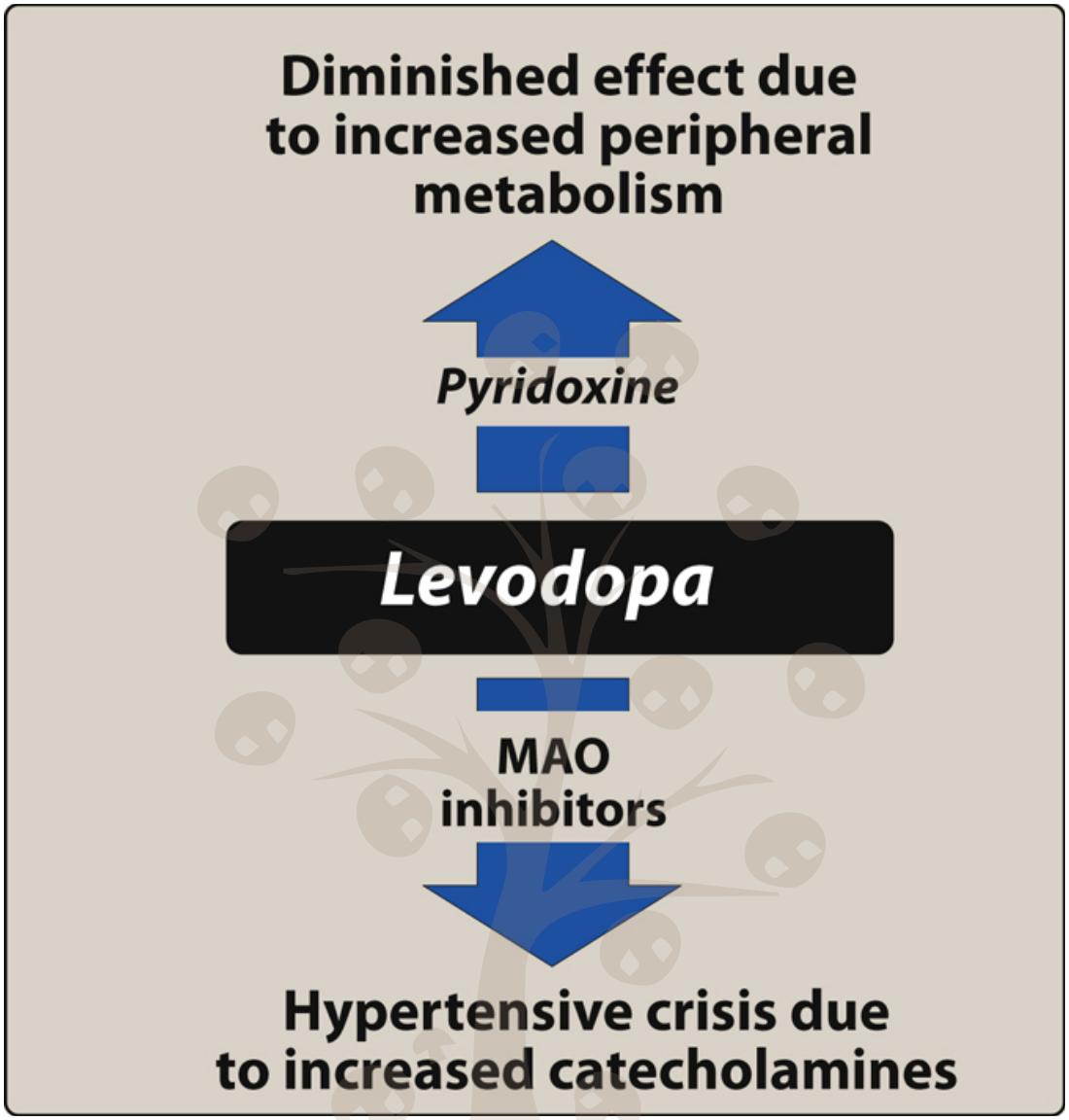

Figure 15.7 Some drug interactions observed with *levodopa*.MAO = monoamine oxidase.

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Clinical Application 15.1: Psychotic Symptoms and Disturbed Behaviors in Parkinson Disease

The presentation of psychotic symptoms and disturbed behaviors in PD may be from two sources: the pathology of the PD or from the treatment of the disease, as most therapies are designed to increase synaptic availability of dopamine. The nonspecific increase in dopamine throughout the brain can contribute to hallucinations and other psychotic symptoms, and yet the treatment of such

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symptoms is often the use of the dopamine receptor-blocking antipsychotic agents, which can in turn inhibit the efficacy of the dopamine-enhancing treatment of the PD. It is a therapeutic challenge to manage the psychiatric symptoms of PD without worsening the movement disorder. *Pimavanserin* and antipsychotics with very weak dopamine antagonism are common agents used in the treatment of PD-related psychosis.

B. Selegiline, rasagiline, and safinamide

Selegiline [se-LE-ji-leen], also called *deprenyl* [DE-pre-nill], selectively inhibits monoamine oxidase (MAO) type B, the enzyme that metabolizes dopamine. It does not inhibit MAO type A (metabolizes norepinephrine and serotonin) unless given above recommended doses, where it loses its selectivity. By decreasing the metabolism of dopamine, *selegiline* increases dopamine levels in the brain (Figure 15.8). When *selegiline* is administered with *levodopa*, it enhances the actions of *levodopa* and substantially reduces the required dose. Unlike nonselective MAOIs, *selegiline* at recommended doses has little potential for causing hypertensive crises. However, the drug loses selectivity at high doses, and therefore the risk of severe hypertension is increased. *Selegiline* is metabolized to *methamphetamine* and *amphetamine*, whose stimulating properties may produce insomnia if the drug is administered later than mid-afternoon. *Rasagiline* [ra-SA-gi-leen], an irreversible and selective inhibitor of brain MAO type B, has five times the potency of *selegiline.* Unlike *selegiline*, *rasagiline* is not metabolized to an *amphetamine*-like substance. *Safinamide* [sa-FIN-a-mide] is also a selective inhibitor of MAO type B indicated for use as an adjunct to *levodopa–carbidopa.* These agents are used as an adjunct to *levodopa* therapy. Adverse effects may include nausea, headache, and confusion. Due to the possibility for precipitating serotonin syndrome, concomitant use with serotonergic agents, such as serotonin reuptake inhibitors, should be avoided.

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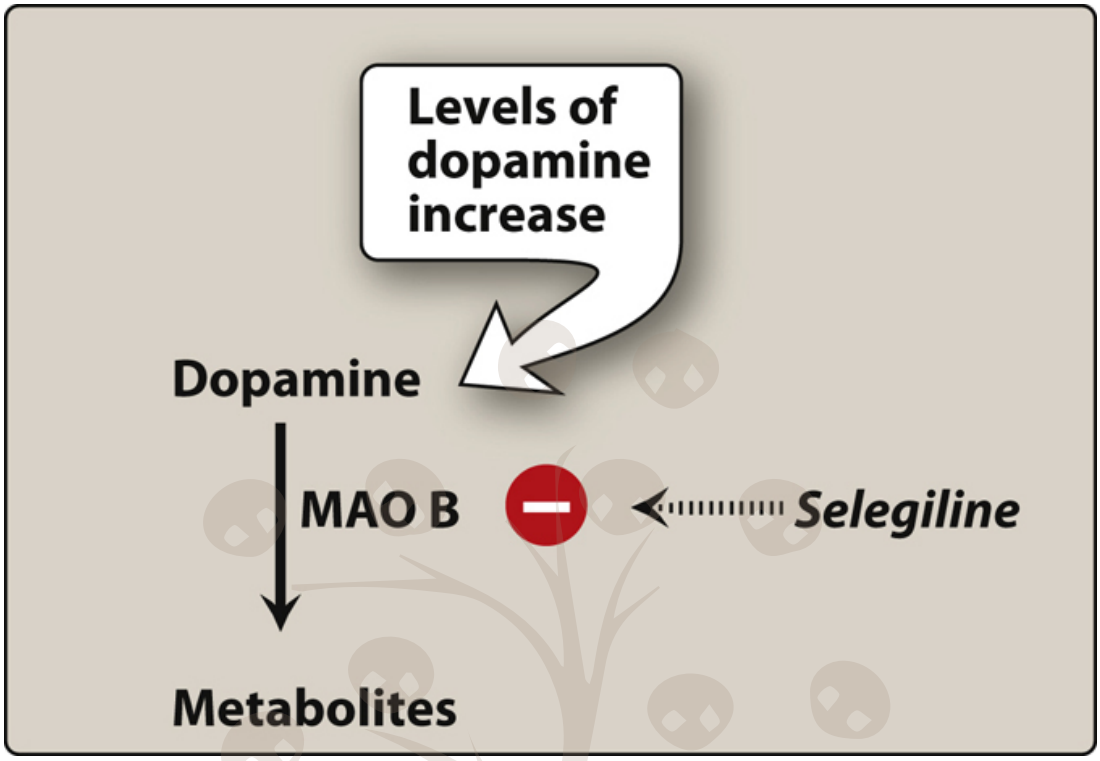

Figure 15.8 Action of *selegiline* (*deprenyl*) in dopamine metabolism.MAO B = monoamine oxidase type B.

C. Catechol-*O*-methyltransferase inhibitors

Normally, the methylation of *levodopa* by catechol-*O*-methyltransferase (COMT) to 3-*O*-methyldopa is a minor pathway for *levodopa* metabolism. However, when peripheral dopamine decarboxylase activity is inhibited by *carbidopa*, a significant concentration of 3-*O*-methyldopa is formed that competes with *levodopa* for active transport into the CNS (Figure 15.9). *Entacapone* [en-TAK-a-pone], *opicapone* [oh-PIK-a-pone], and *tolcapone* [TOLE-ka-pone] selectively and reversibly inhibit COMT. Inhibition of COMT by these agents leads to decreased plasma concentrations of 3-*O*-methyldopa, increased central uptake of *levodopa*, and greater concentrations of brain dopamine. These agents reduce the symptoms of "wearing off" phenomena seen in patients on

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levodopa–carbidopa. The drugs differ primarily in their pharmacokinetic and adverse effect profiles.

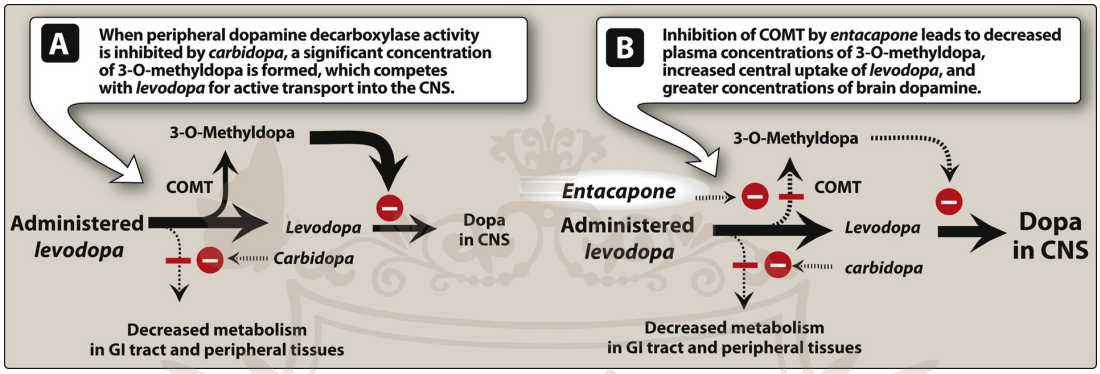

Figure 15.9 Effect of *entacapone* on dopa concentration in the central nervous system (CNS).COMT = catechol-*O*-methyltransferase.

1.Pharmacokinetics: Oral absorption of *entacapone* and *tolcapone* occurs readily and is not influenced by food. *Opicapone* should be taken on an empty stomach. Patients should not eat food within 1 hour before or after administration. These agents are extensively bound to plasma albumin, with a limited volume of distribution. *Tolcapone* has a relatively long duration of action (probably due to its affinity for COMT) compared with *entacapone*, although both drugs require multiple daily dosing. *Opicapone* is administered once daily at bedtime. These drugs are extensively metabolized and eliminated in feces and urine. The dosage may need to be adjusted in patients with moderate or severe hepatic impairment.

2.Adverse effects: The COMT inhibitors exhibit adverse effects that are commonly observed in patients taking *levodopa–carbidopa*, including diarrhea, postural hypotension, nausea, anorexia, dyskinesias, hallucinations, and sleep disorders. Most seriously, fulminating hepatic necrosis is associated with *tolcapone* use. Therefore, along with

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appropriate hepatic function monitoring, it should only be used in patients in whom other modalities have failed. *Entacapone* and *opicapone* do not exhibit this toxicity and have largely replaced *tolcapone* in clinical practice.

D. Dopamine receptor agonists

This group of antiparkinsonian compounds includes *bromocriptine* [broe-moe-KRIP-teen], an ergot derivative, and the nonergot drugs, *ropinirole* [roe-PIN-i-role], *pramipexole* [pra-mi-PEX-ole], *rotigotine* [ro-TIG-oh-teen], and *apomorphine* [a-poe-MOR-feen]. These agents have a longer duration of action than that of *levodopa* and are effective in patients exhibiting fluctuations in response to *levodopa.* Initial therapy with these drugs is associated with less risk of developing dyskinesias and motor fluctuations as compared with patients started on *levodopa. Bromocriptine*, *pramipexole*, and *ropinirole* are effective in patients with PD complicated by motor fluctuations and dyskinesias. However, these drugs are ineffective in patients who have not responded to *levodopa.* Injectable *apomorphine* is a dopamine agonist that is used in severe and advanced stages of the disease to supplement oral medications. Adverse effects severely limit the utility of the dopamine agonists and may include nausea, vomiting, somnolence, and postural hypotension (Figure 15.10). These agents may be associated with a loss of impulse control, which can lead to compulsive behaviors such as uncontrolled spending, increased libido, or binge eating.

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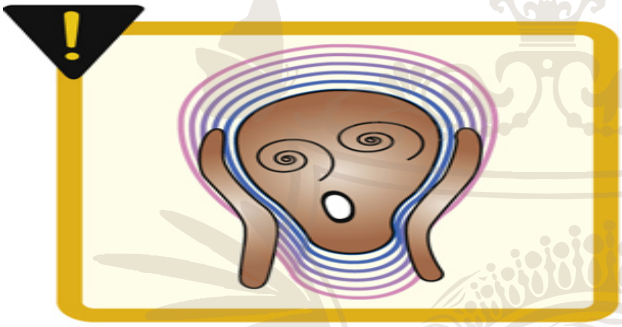
Sedation



Hallucinations

Confusion

Nausea

Hypotension

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Figure 15.10 Some adverse effects of dopamine agonists.

1.Bromocriptine: The actions of the ergot derivative *bromocriptine* are similar to those of *levodopa*, except that hallucinations, confusion, delirium, nausea, and orthostatic hypotension are more common, whereas dyskinesia is less prominent. In psychiatric illness, *bromocriptine* may cause the mental condition to worsen. It should be used with caution in patients with a history of myocardial infarction or peripheral vascular disease due to the risk of vasospasm. Because *bromocriptine* is an ergot derivative, it has the potential to cause pulmonary and retroperitoneal fibrosis.

2.Apomorphine, pramipexole, ropinirole, and rotigotine: These are nonergot dopamine agonists that are approved for the treatment of PD. [Note: *Pramipexole, ropinirole*, and *rotigotine* are also indicated for the treatment of restless legs syndrome.] *Pramipexole* and *ropinirole* are orally active agents. *Apomorphine* is available in injectable and sublingual formulations, and *rotigotine* is available as a transdermal delivery system. *Apomorphine* is used for acute management of the hypomobility "off" phenomenon in advanced PD. *Rotigotine* is administered as a once-daily transdermal patch that provides even drug levels over 24 hours. These agents alleviate the motor deficits in patients who have never taken *levodopa* and also in patients with advanced PD who are treated with *levodopa.* Dopamine agonists may delay the need to use *levodopa* in early PD and may decrease the dose of *levodopa* in advanced PD. Unlike the ergotamine derivatives, these agents do not exacerbate peripheral vascular disorders or cause fibrosis. Nausea, hallucinations, compulsive behaviors, insomnia, dizziness, constipation, and orthostatic hypotension are adverse effects of these drugs, but dyskinesias are less frequent than with

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levodopa (Figure 15.11). *Pramipexole* is mainly excreted unchanged in the urine, and dosage adjustments are needed in renal dysfunction. The fluoroquinolone antibiotics and other inhibitors of the cytochrome P450 (CYP450) 1A2 isoenzyme (for example, *fluvoxamine*) may inhibit the metabolism of *ropinirole*, requiring an adjustment in *ropinirole* dosage. Figure 15.12 summarizes some properties of dopamine agonists.

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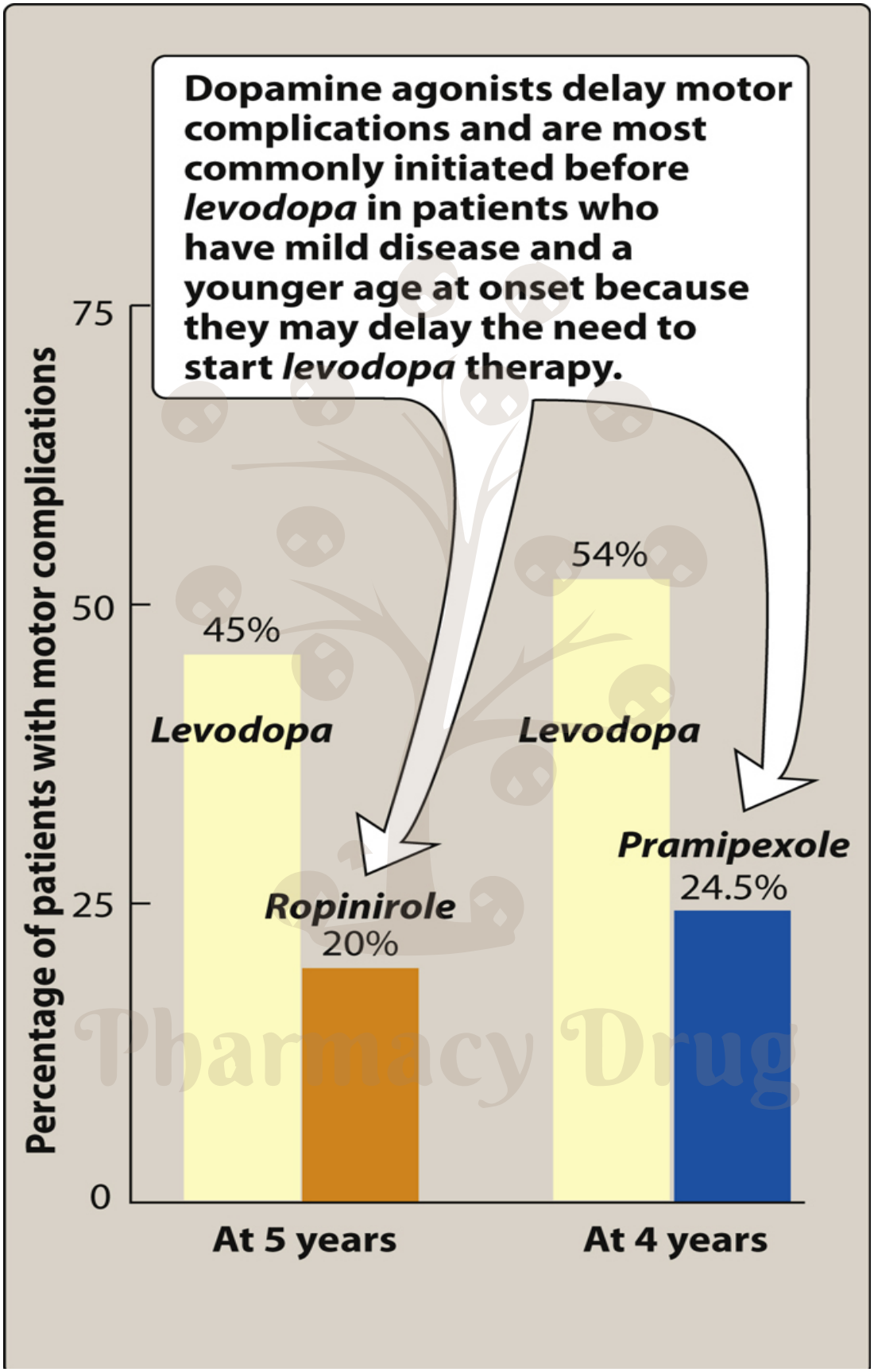

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Figure 15.11 Motor complications in patients treated with *levodopa* or dopamine agonists.

Characteristic	*Pramipexole*	*Ropinirole*	*Rotigotine*
Bioavailability	>90%	55%	45%
V_d	7 L/kg	7.5 L/kg	84 L/kg
Half-life	8 h[1]	6 h	7 h[3]
Metabolism	Negligible	Extensive	Extensive
Elimination	Renal	Renal[2]	Renal[2]

Figure 15.12 Pharmacokinetic properties of dopamine agonists *pramipexole*, *ropinirole*, and *rotigotine*. V_d = volume of distribution.

[1]Increases to 12 hours in patients older than 65 years. [2]Less than 10% excreted unchanged. [3]Administered as a once-daily transdermal patch.

E. Amantadine

It was accidently discovered that the antiviral drug *amantadine* [a-MAN-ta-deen] has an antiparkinsonian action. *Amantadine* has several effects on a number of neurotransmitters implicated in parkinsonism, including increasing the release of dopamine, blocking cholinergic receptors, and inhibiting the *N*-methyl-d-aspartate (NMDA) type of glutamate receptors. The drug may cause restlessness, agitation, confusion, and hallucinations, and at high doses, it may induce acute toxic psychosis. Orthostatic hypotension, urinary retention, peripheral edema, and dry mouth also may occur. *Amantadine* is less efficacious than *levodopa*, and tolerance develops more readily. However, *amantadine* has fewer adverse effects.

F. Antimuscarinic agents

The antimuscarinic agents are much less efficacious than *levodopa* and play only an adjuvant role in antiparkinsonism

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therapy. The actions of *benztropine* [BENZ-troe-peen] and *trihexyphenidyl* [tri-hex-ee-FEN-i-dill] are similar, although individual patients may respond more favorably to one drug or the other. Blockade of cholinergic transmission produces effects similar to augmentation of dopaminergic transmission, since it helps to correct the imbalance in the dopamine/acetylcholine activity (Figure 15.4). These agents can induce mood changes and confusion and produce xerostomia, constipation, and visual problems typical of muscarinic blockers (see Chapter 5). They interfere with gastrointestinal peristalsis and are contraindicated in patients with glaucoma, prostatic hyperplasia, or pyloric stenosis.

G. Adenosine receptor antagonist

Istradefylline [IS-tra-DEF-i-lin] is indicated as an adjuvant to *levodopa/carbidopa* therapy for the symptomatic management of PD to reduce the frequency and length of off episodes. The proposed mechanism of action for this agent is antagonism of the adenosine A_{2A} receptor. Adverse events that may occur with use are dyskinesias, nausea, constipation, hallucinations, insomnia, and loss of impulse control.

VII. DRUGS USED IN ALZHEIMER DISEASE

Dementia of the Alzheimer type has three distinguishing features: (1) accumulation of amyloid beta plaques in the brain, (2) formation of numerous neurofibrillary tangles (tau protein accumulations), and (3) loss of cortical neurons, particularly cholinergic neurons. Current therapies aim to improve cholinergic transmission within the CNS, prevent excitotoxic actions resulting from overstimulation of NMDA-glutamate receptors in selected areas of the brain, or reduce accumulation of amyloid beta plaques. In general, pharmacologic intervention for AD is only palliative and provides modest short-term benefits by lessening or stabilizing symptoms.

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A. Acetylcholinesterase inhibitors

Numerous studies have linked the progressive loss of cholinergic neurons and, presumably, cholinergic transmission within the cortex to the memory loss that is a hallmark symptom of AD. It is postulated that inhibition of acetylcholinesterase (AChE) within the CNS improves cholinergic transmission, at least at those neurons that are still functioning. The reversible AChE inhibitors approved for the treatment of AD include *donepezil* [doe-NE-peh-zil], *galantamine* [ga-LAN-ta-meen], and *rivastigmine* [ri-va-STIG-meen]. These agents have some selectivity for AChE in the CNS, as compared with the periphery. *Galantamine* may also augment the action of acetylcholine at nicotinic receptors in the CNS. At best, these compounds may provide a modest reduction in the rate of loss of cognitive functioning in Alzheimer patients. *Donepezil* is generally preferred since it can be given once daily. *Rivastigmine* is the only agent approved for the management of dementia associated with PD and also the only AChE inhibitor available as a transdermal formulation. *Rivastigmine* is hydrolyzed by AChE to a carbamylated metabolite and has no interactions with drugs that alter the activity of CYP450 enzymes. The other agents are substrates for CYP450 and have a potential for such interactions. Common adverse effects include nausea, diarrhea, vomiting, anorexia, tremors, bradycardia, and muscle cramps (Figure 15.13).

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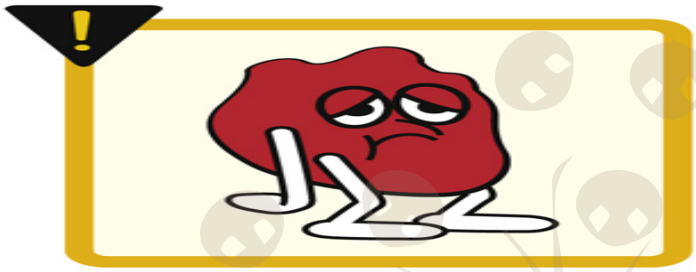
Tremors



Bradycardia

Nausea

Diarrhea

Anorexia

Myalgia

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Figure 15.13 Adverse effects of AChE inhibitors.

Clinical Application 15.2: The Use of Acetylcholinesterase Inhibitors in Alzheimer Disease

When acetylcholinesterase inhibitors are used in the treatment of AD, the patient may experience nausea, vomiting, enuresis, and diarrhea. Common medications used to manage these side effects may have anticholinergic properties as part of their therapeutic profile. The prescriber must keep in mind that some of these strategies to treat the peripheral cholinergic adverse effects secondary to acetylcholinesterase inhibitors may also negatively affect cognition. This can occur because these agents can cross the blood–brain barrier and may interfere with the intent to increase CNS acetylcholine synaptic activity.

B. NMDA receptor antagonist

Stimulation of glutamate receptors in the CNS appears to be critical for the formation of certain memories. However, overstimulation of glutamate receptors, particularly of the NMDA type, may result in excitotoxic effects on neurons and is suggested as a mechanism for neurodegenerative or apoptotic (programmed cell death) processes. Binding of glutamate to the NMDA receptor assists in the opening of an ion channel that allows Ca^{2+} to enter the neuron. Excess intracellular Ca^{2+} can activate a number of processes that ultimately damage neurons and lead to apoptosis. *Memantine* [meh-MAN-teen] is an NMDA receptor antagonist indicated for moderate to severe AD. It acts by blocking the NMDA receptor and limiting Ca^{2+} influx into the neuron, such that toxic intracellular levels are not achieved. *Memantine* is well tolerated, with few dose-dependent adverse events. Expected adverse effects, such as confusion, agitation, and restlessness, are often indistinguishable from the symptoms of AD. Given its different mechanism of action and possible

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neuroprotective effects, *memantine* is often given in combination with an AChE inhibitor.

C. Aducanumab

Aducanumab [add-yoo-CAN-yoo-mab] is an amyloid beta–directed monoclonal antibody administered intravenously for the treatment of AD. *Aducanumab* reduces amyloid beta plaques in the brain, although it is uncertain if it delays disease progression. Adverse effects include amyloid-related imaging abnormalities such as brain edema or microhemorrhage, headache, and diarrhea.

VIII. DRUGS USED IN MULTIPLE SCLEROSIS

MS is an autoimmune inflammatory demyelinating disease of the CNS. The course of MS is variable. For some, MS may consist of one or two acute neurologic episodes. In others, it is a chronic, relapsing, or progressive disease that may span 10 to 20 years. Historically, corticosteroids (for example, *dexamethasone, methylprednisolone,* and *prednisone*) have been used to treat acute exacerbations of the disease. Chemotherapeutic agents, such as *cyclophosphamide* and *azathioprine*, have also been used.

A. Disease-modifying therapies

Drugs currently approved for MS are indicated to decrease relapse rates or, in some cases, to prevent accumulation of disability (Figure 15.14). The major target of these medications is to modify the immune response through inhibition of white blood cell–mediated inflammatory processes that eventually lead to myelin sheath damage and decreased or inappropriate axonal communication between cells.

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DRUGS FOR MULTIPLE SCLEROSIS

Alemtuzumab LEMTRADA
Azathioprine AZASAN, IMURAN
Cladribine MAVENCLAD
Cyclophosphamide GENERIC ONLY
Dalfampridine AMPYRA
Dexamethasone DECADRON
Dimethyl fumarate TECFIDERA
Diroximel fumarate VUMERITY
Fingolimod GILENYA
Glatiramer COPAXONE
Interferon beat-1a AVONEX, REBIF
Interferon beat-1b BETASERON, EXTAVIA
Monomethyl fumarate BAFIERTAM
Natalizumab TYSABRI
Ocrelizumab OCREVUS
Ofatumumab KESIMPTA
Ozanimod ZEPOSIA
Ponesimod PONVORY
Prednisone DELTASONE
Siponimod MAYZENT
Teriflunomide AUBAGIO

DRUGS FOR ALS

Edaravone RADICAVA
Riluzole RILUTEK

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Figure 15.14 Drugs used in the treatment of multiple sclerosis and amyotrophic lateral sclerosis (ALS).

1. **Interferon beta-1a and interferon beta-1b:** The immunomodulatory effects of injectable *interferon* [in-ter-FEER-on] help to diminish the inflammatory responses that lead to demyelination of the axon sheaths. Adverse effects of these medications may include depression, local injection site reactions, increase in hepatic enzymes, and flu-like symptoms.

2. **Glatiramer:** *Glatiramer* [gluh-TEER-a-mur] is a synthetic polypeptide that resembles myelin protein and may act as a decoy to T cell attack. Some patients experience a postinjection reaction that includes flushing, chest pain, anxiety, and itching. It is usually self-limiting.

3. **Sphingosine 1-phosphate receptor modulators:** *Fingolimod* [fin-GO-li-mod], *ozanimod* [oh-ZAN-i-mod], *ponesimod* [poe-NES-i-mod], and *siponimod* [si-PON-i-mod] are oral drugs that alter lymphocyte migration by modulating the sphingosine 1-phosphate (S1P) receptor, thereby resulting in fewer lymphocytes in the CNS. *Fingolimod* may cause first-dose bradycardia requiring an observation period of at least 6 hours after administration. *Fingolimod* and the other S1P receptor modulators are associated with an increased risk of macular edema. These agents also carry an increased risk for opportunistic infections and progressive multifocal leukoencephalopathy (PML), a rare but aggressive and potentially fatal disease that attacks the brain. *Ozanimod* is a substrate of CYP2C8, and coadministration with strong CYP2C8 inducers or inhibitors is not recommended. Genetic testing for polymorphisms of the CYP2C9 enzyme is required to adjust dosing for *siponimod*, as CYP2C9 is the primary enzyme for metabolism of the drug. Expression of the CYP2C9*3/*3 genotype is a contraindication to use of this

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agent, because of the potential for significantly elevated levels of *siponimod.*

4. **Teriflunomide:** *Teriflunomide* [ter-i-FLOO-noe-mide] is an oral pyrimidine synthesis inhibitor that leads to a lower concentration of active lymphocytes in the CNS. *Teriflunomide* may cause elevated liver enzymes. It should be avoided in pregnancy.

5. **Nuclear factor (erythroid-derived 2)-like 2 activators:** *Dimethyl fumarate* [dye-METH-il FUE-mar-ate], *diroximel* [dye-ROX-i-mel] *fumarate,* and *monomethyl* [MON-oh-METH-il] *fumarate* are oral agents that activate the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) antioxidant response pathway. This action may alter the cellular response to oxidative stress to reduce disease progression in MS. Flushing, abdominal pain, diarrhea, and nausea are the most common adverse events. An increased risk for opportunistic infections, including PML and liver injury, is a warning for these agents.

6. **Monoclonal antibodies:** *Alemtuzumab* [AL-em-TOOZ-ue-mab], *natalizumab* [na-ta-LIZ-ue-mab], *ocrelizumab* [OK-re-LIZ-ue-mab], and *ofatumumab* [OH-fa-TOO-mue-mab] are monoclonal antibodies indicated for the treatment of MS that target different steps in the immune response involving lymphocytes or leukocytes. [Note: *Rituximab* may also be used off-label for the treatment of MS.] *Ocrelizumab* is the first agent to be approved for primary progressive forms of the disease. These agents can be associated with significant adverse effects, such as PML and other serious infections, and autoimmune disorders with *alemtuzumab.* As such, these agents may be reserved for patients who have failed other therapies.

Natalizumab is a recombinant monoclonal antibody that can be used as monotherapy for the treatment of relapsing forms of

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MS. It is also used in the management of Crohn disease. *Natalizumab* is directed against the alpha-4 subunit of integrin molecules. It blocks the integrin association with receptors on vascular endothelial cells to limit the adhesion and transmigration of leukocytes. This agent is administered by intravenous (IV) infusion. Adverse effects may include infusion-related reactions, arthralgia, gastrointestinal distress, rash, and increased risk of infection. Due to the increased risk for PML, it is available only through a distribution program.

Ocrelizumab is an anti-CD20 monoclonal antibody with a similar mechanism of action to *rituximab.* It binds to a different CD20 epitope than *rituximab* and can enhance B cell depletion. *Ocrelizumab* can be used for the treatment of relapsing forms of MS, as well as primary progressive MS. It is administrated by IV infusion. Adverse effects may include infusion reactions and an increased risk of infection, especially skin and respiratory tract infections. *Ofatumumab* is also an anti-CD20 monoclonal antibody that leads to selective B cell depletion. It is indicated for relapsing forms of MS and can be given by IV infusion or subcutaneous injection. Adverse effects may include headache, rash, infusion or injection-site reactions, and increased risk of upper respiratory infections.

Alemtuzumab is an anti-CD52 monoclonal antibody that causes depletion of CD52-expressing T cells, B cells, natural killer cells, and monocytes. It can be used in the management of relapsing forms of MS, but due to its potential for serious adverse effects it is reserved for severe cases that may not be responsive to other therapy. This agent can cause headache, rash, and gastrointestinal distress. In addition, it has boxed warnings for autoimmune effects, infusion reactions, new malignancies, and stroke. Due to these risks, it is available only through a restricted distribution program.

7.Cladribine: *Cladribine* [KLAD-ri-been] is a purine analogue that serves as an antimetabolite. The drug interferes with enzymes that are needed for DNA synthesis and causes

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cytotoxic effects on B and T lymphocytes, resulting in their depletion. *Cladribine* may cause liver injury and an increased risk for infections. Malignancies and teratogenicity are serious warnings for this agent, and it should be avoided in pregnancy.

B. Symptomatic treatment

Many different classes of drugs are used to manage symptoms of MS such as spasticity, constipation, bladder dysfunction, and depression. *Dalfampridine* [DAL-fam-pre-deen], an oral potassium channel blocker, improves walking speeds in patients with MS. It is the first drug approved for this use.

Clinical Application 15.3: Risk of Infection with Multiple Sclerosis Pharmacologic Therapy

To manage and slow the progression of MS, most of the available agents act as modulators or inhibitors of certain immune responses. As a result, many of the agents for MS increase the risk of opportunistic infections (for example, PML, cytomegalovirus, or cryptococcal meningitis) or prevent the body from properly mounting a full response to infectious processes. Both clinicians and the patients taking these medications must be vigilant regarding this increased risk and the potential problems that this can cause for a patient on long-term therapy for MS.

IX. DRUGS USED IN AMYOTROPHIC LATERAL SCLEROSIS

ALS, also referred to as Lou Gehrig disease, is characterized by progressive degeneration of motor neurons, resulting in the inability to initiate or control muscle movement. *Riluzole* [RIL-ue-zole] and *edaravone* [e-DAR-a-vone] are indicated for the management of ALS. *Riluzole* is a glutamate modulator that is believed to act by inhibiting glutamate release and blocking sodium channels. *Riluzole* may improve survival time in patients suffering from ALS. Adverse effects may include nausea, dizziness, weakness, and increased

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liver enzymes. *Edaravone* is an intravenous free radical scavenger and antioxidant that may slow the progression of ALS. Adverse effects of this agent may include an abnormal gait, bruising, and headache.

Chapter Summary

- Progressive neurodegenerative diseases such as Parkinson disease (PD), Alzheimer disease (AD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) currently have no curative treatments. Pharmacotherapy is targeted to slow disease progression and manage symptoms to achieve optimal quality of life.
- PD is believed to be due to a loss of dopamine-producing neurons in the substantia nigra area of the basal ganglia, resulting in progressive loss of motor control and balance for the patient.
- As the condition progresses, the management of PD may result in multiple agents being used, each with a different mechanism of action. They typically increase the availability of dopamine or the signaling of the dopamine receptors.
- AD is believed to result from cholinergic neuronal loss, which is likely due to the accumulation of beta-amyloid plaques and/or tau protein that results in neuronal cell death.
- Acetylcholinesterase inhibitors (*donepezil*, *galantamine*, and *rivastigmine*) are the mainstay of therapy for AD. These agents inhibit enzymatic breakdown of acetylcholine, thus making more acetylcholine available in the synaptic cleft to address the cognitive impairment related to the loss of cholinergic neuronal activity.
- *Memantine*, an NMDA receptor antagonist, is often combined with an acetylcholinesterase inhibitor in the treatment of moderate to severe AD.
- A variety of medications have been developed for MS to manage and address the relapsing patient; however, many of these treatments are infusions requiring professional administration and supervision. Most of the pharmacological treatments of MS modify and inhibit some immune responses, thus increasing the risk for infections.

STUDY QUESTIONS

Choose the ONE best answer.

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15.1 A 75-year-old man has moderate Parkinson disease. His tremors and bradykinesia are no longer responding to anticholinergic treatment. Which combination of antiparkinsonian drugs is an appropriate treatment plan?

A. Amantadine, carbidopa, and entacapone
B. Levodopa, carbidopa, and entacapone
C. Pramipexole, carbidopa, and entacapone
D. Ropinirole, carbidopa, and selegiline

Correct answer = B. To reduce the dose of levodopa and its peripheral side effects, the peripheral decarboxylase inhibitor, carbidopa, is coadministered. As a result of this combination, more levodopa is available for metabolism by catechol-*O*-methyltransferase (COMT) to 3-*O*-methyldopa, which competes with levodopa for the active transport processes into the CNS. By administering entacapone (an inhibitor of COMT), the competing product is not formed, and more levodopa enters the brain. The other choices are not appropriate because neither peripheral decarboxylase nor COMT nor monoamine oxidase metabolizes amantadine or the direct-acting dopamine agonists ropinirole and pramipexole; thus, carbidopa and entacapone should only be given with levodopa, otherwise they are not contributing to the clinical response of the patient.

15.2 Which drug used in the management of Parkinson disease may cause vasospasm?

A. Amantadine
B. Bromocriptine
C. Entacapone
D. Ropinirole

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Correct answer = B. Bromocriptine is a dopamine receptor agonist that may cause vasospasm. It is contraindicated in patients with peripheral vascular disease. Ropinirole directly stimulates dopamine receptors, but it does not cause vasospasm. The other drugs do not act directly on dopamine receptors.

15.3 Modest improvement in the memory of patients with Alzheimer disease may occur with drugs that increase

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transmission at which receptor?

A. Adrenergic
B. Cholinergic
C. Dopaminergic
D. Serotonergic

Correct answer = B. AChE inhibitors, such as galantamine, increase cholinergic transmission in the CNS and may cause a modest delay in the progression of Alzheimer disease. Increased transmission at the other types of receptors listed does not result in improved memory.

15.4 A 70-year-old woman with moderate to severe dementia related to Alzheimer disease has been treated with an acetylcholinesterase inhibitor for 6 months at maximum dosing with minimal effect. Which medication is a glutamate receptor antagonist that could provide added benefit for management of her moderate to severe symptoms of Alzheimer disease?

A. Rivastigmine
B. Pramipexole
C. Memantine
D. Galantamine

Correct answer = C. When combined with an acetylcholinesterase inhibitor, memantine has modest efficacy in keeping patients with Alzheimer disease at or above baseline for at least 6 months and may delay disease progression. It is currently not approved for mild cognitive impairment or mild AD.

15.5 Which medication would benefit a 55-year-old woman recently diagnosed with amyotrophic lateral sclerosis (ALS)?

A. Cladribine
B. Galantamine
C. Riluzole
D. Prednisone

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Correct answer = C. Riluzole is approved for the debilitating illness of ALS. It is used to delay the progression and need for ventilator support in severe patients. It is believed to work by decreasing the release of glutamate from the presynaptic terminal.

15.6 A 48-year-old woman with relapsing multiple sclerosis has had intolerable adverse reactions to interferon beta (depression) and dimethyl fumarate (angioedema) and now requires an alternative treatment option. Which medication is most appropriate for this patient?

A. Edaravone
B. Monomethyl fumarate
C. Teriflunomide
D. Galantamine

Correct answer = C. Teriflunomide may provide an alternative treatment option with a different side effect profile compared with the prior two attempted treatments. If the patient is of childbearing potential, then she should be warned of the risk for teratogenicity. Monomethyl fumarate is the active metabolite of dimethyl fumarate and carries the same risks to this patient as the dimethyl fumarate. Edaravone and galantamine are not indicated for the treatment of multiple sclerosis.

15.7 Which agent may cause tremors as an adverse effect and should be used with caution in patients with Parkinson disease, even though it is also indicated for the treatment of dementia associated with Parkinson disease?

A. Benztropine
B. Rotigotine
C. Rivastigmine
D. Trihexyphenidyl

Correct answer = C. Although rivastigmine is an acetylcholinesterase inhibitor, which can cause tremors as an adverse effect, its use is not contraindicated in patients with Parkinson disease, as this agent is also the only medication

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approved for dementia associated with Parkinson disease. It should be used with caution, as it may worsen the parkinsonian-related tremors. A risk–benefit discussion should occur with the patient and the caregiver before rivastigmine is used. Rotigotine, benztropine, and trihexyphenidyl are treatments to improve tremors in PD.

15.8 A 45-year-old woman presents to the emergency room with debilitating gait dysfunction, numbness across the lower extremities, urinary incontinence, and fatigue. Her past medical history is otherwise negative and she does not take any medications. Imaging and laboratory tests confirm a diagnosis of multiple sclerosis. Which agent could be used to manage this acute exacerbation of multiple sclerosis for the patient?

A. Siponimod
B. Methylprednisolone
C. Cladribine
D. Ofatumumab

Correct answer = B. The corticosteroids such as methylprednisolone IV for 3 to 5 days are recommended for acute exacerbations, whereas the other agents, siponimod, cladribine, and ofatumumab, are indicated for relapse prevention or reduction in frequency of relapses.

15.9 A 75-year-old man presents to his neurologist for the management of newly diagnosed mild dementia of the Alzheimer type. The physician would like to prescribe an acetylcholinesterase inhibitor. Which agent would be the best option to initiate for treatment?

A. Glatiramer
B. Memantine
C. Galantamine
D. Selegiline

Correct answer = C. Galantamine is the only acetylcholinesterase inhibitor and is indicated for mild to moderate AD. Although memantine is indicated for

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moderate to severe AD, it is an NMDA antagonist. Glatiramer is indicated for MS, and selegiline is indicated for PD.

15.10 A 39-year-old man presents to his neurologist for the management of multiple sclerosis. He has a history of JC virus–induced progressive multifocal leukoencephalopathy (PML) from the use of alemtuzumab and now requires an alternative treatment with no increased risk for the development of PML. Which agent has the lowest risk for PML and would be an effective treatment option for MS?

A. Fingolimod
B. Ocrelizumab
C. Natalizumab
D. Interferon beta-1a

Correct answer = D. Interferons have no increased risk for the development of PML, whereas the other listed disease-modifying medications, fingolimod, ocrelizumab, and natalizumab, all carry an increased risk for this dangerous opportunistic infection and disease.

POLE STAR

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16

Anxiolytic and Hypnotic Drugs

Jose A. Rey

I. OVERVIEW

Disorders involving anxiety are among the most common mental disorders. Anxiety is an unpleasant state of tension, apprehension, or uneasiness (a fear that arises from either a known or an unknown source). The physical symptoms of severe anxiety are similar to those of fear (such as tachycardia, sweating, trembling, and palpitations) and involve sympathetic activation. Episodes of mild anxiety are common life experiences and do not warrant treatment. However, severe, chronic, debilitating anxiety may be treated with antianxiety drugs (sometimes called anxiolytics) and/or some form of psychotherapy. Because many antianxiety drugs also cause some sedation, they may be used clinically as both anxiolytic and hypnotic (sleep-inducing) agents. Figure 16.1 summarizes the anxiolytic and hypnotic agents. Some antidepressants are also indicated for certain anxiety disorders; however, they are discussed with the antidepressants (see Chapter 17).

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BENZODIAZEPINES

Alprazolam XANAX
Chlordiazepoxide LIBRIUM
Clonazepam KLONOPIN
Clorazepate TRANXENE
Diazepam VALIUM, DIASTAT
Estazolam GENERIC ONLY
Flurazepam GENERIC ONLY
Lorazepam ATIVAN
Midazolam GENERIC ONLY
Oxazepam GENERIC ONLY
Quazepam DORAL
Temazepam RESTORIL
Triazolam HALCION

BENZODIAZEPINE ANTAGONIST

Flumazenil GENERIC ONLY

OTHER ANXIOLYTIC DRUGS

Antidepressants VARIOUS (SEE CHAPTER 17)
Buspirone GENERIC ONLY
Meprobamate GENERIC ONLY

BARBITURATES

Amobarbital AMYTAL
Methohexital BREVITAL
Pentobarbital NEMBUTAL
Phenobarbital GENERIC ONLY
Secobarbital SECONAL

OTHER HYPNOTIC AGENTS

Antihistamines VARIOUS (SEE CHAPTER 39)
Doxepin SILENOR
Eszopiclone LUNESTA
Lemborexant DAYVIGO
Ramelteon ROZEREM
Suvorexant BELSOMRA
Tasimelteon HETLIOZ
Zaleplon SONATA
Zolpidem AMBIEN, ZOLPIMIST

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Figure 16.1 Summary of anxiolytic and hypnotic drugs.

II. BENZODIAZEPINES

Benzodiazepines are widely used anxiolytic drugs. They replaced barbiturates and *meprobamate* in the treatment of anxiety and insomnia, because benzodiazepines are generally considered to be safer and more effective (Figure 16.2). Although benzodiazepines are commonly used, they are often not the drug of choice for treating either anxiety or insomnia. Certain antidepressants with anxiolytic action, such as the selective serotonin reuptake inhibitors, are preferred in many cases for management of anxiety, and nonbenzodiazepine hypnotics and antihistamines may be preferable for insomnia.

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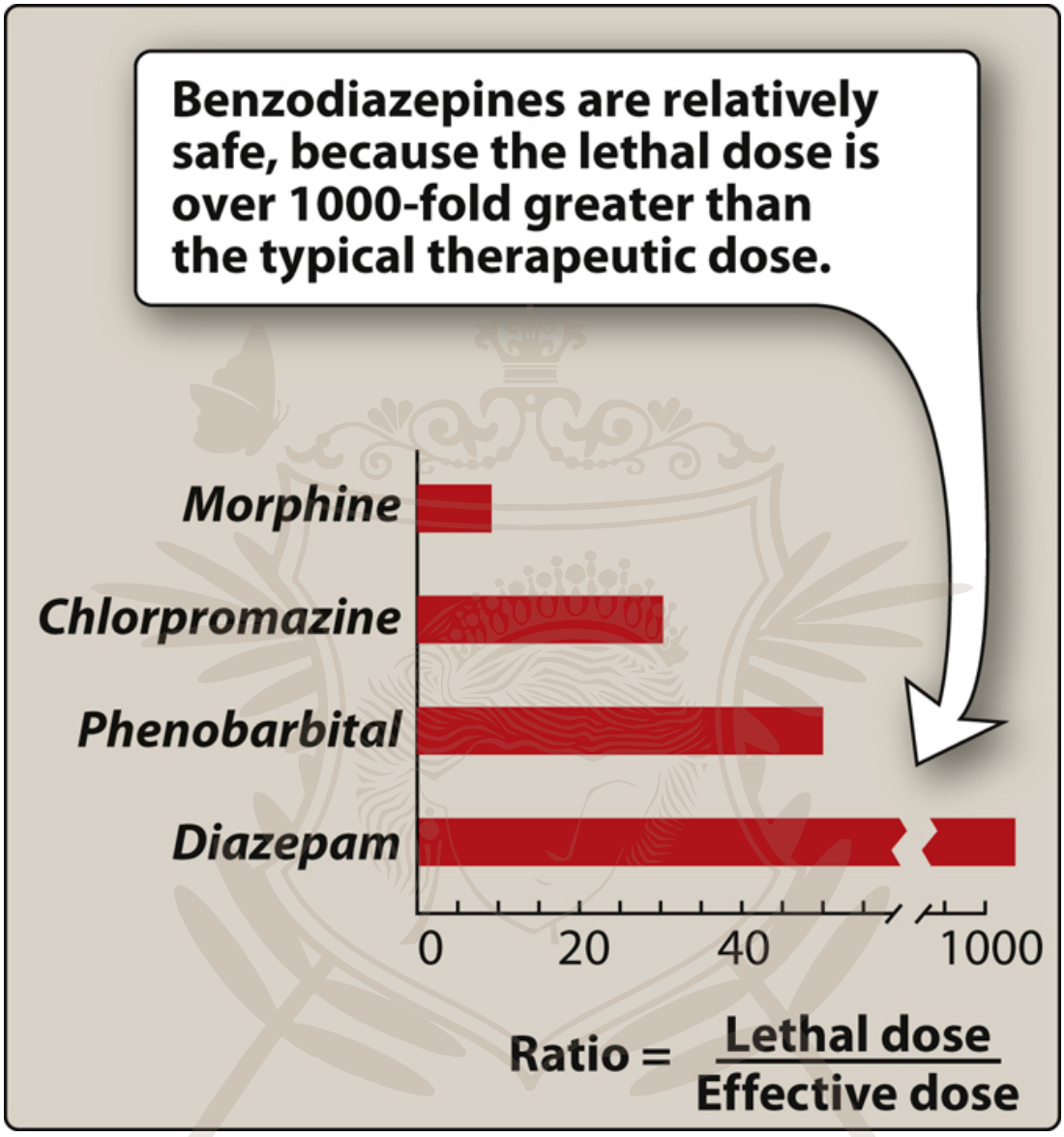

Figure 16.2 Ratio of lethal dose to effective dose for *morphine* (an opioid, see Chapter 21), *chlorpromazine* (an antipsychotic, see Chapter 18), and the anxiolytic, hypnotic drugs, *phenobarbital* and *diazepam*.

POLE STAR

A. Mechanism of action

The action of the benzodiazepines is mediated via the inhibitory neurotransmitter γ-aminobutyric acid (GABA) in the central nervous system (CNS). Benzodiazepines preferentially target GABA subtype A ($GABA_A$) receptors. The $GABA_A$ receptors are

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composed of a combination of five α, β, and γ subunits that span the postsynaptic membrane (Figure 16.3). For each subunit, many subtypes exist (for example, there are six subtypes of the α subunit). Binding of GABA to its receptor triggers an opening of the central ion channel, allowing chloride ions to transit through the pore. The influx of chloride ions causes hyperpolarization of the neuron and decreases neurotransmission by inhibiting the formation of action potentials. Benzodiazepines modulate GABA effects by binding to a specific, high-affinity site (distinct from the GABA-binding site) located at the interface of the α subunit and the γ subunit on the $GABA_A$ receptor (Figure 16.3). Benzodiazepines increase the frequency of channel openings produced by GABA. The clinical effects of individual benzodiazepines correlate well with the binding affinity of each drug for the GABA receptor–chloride ion channel complex.

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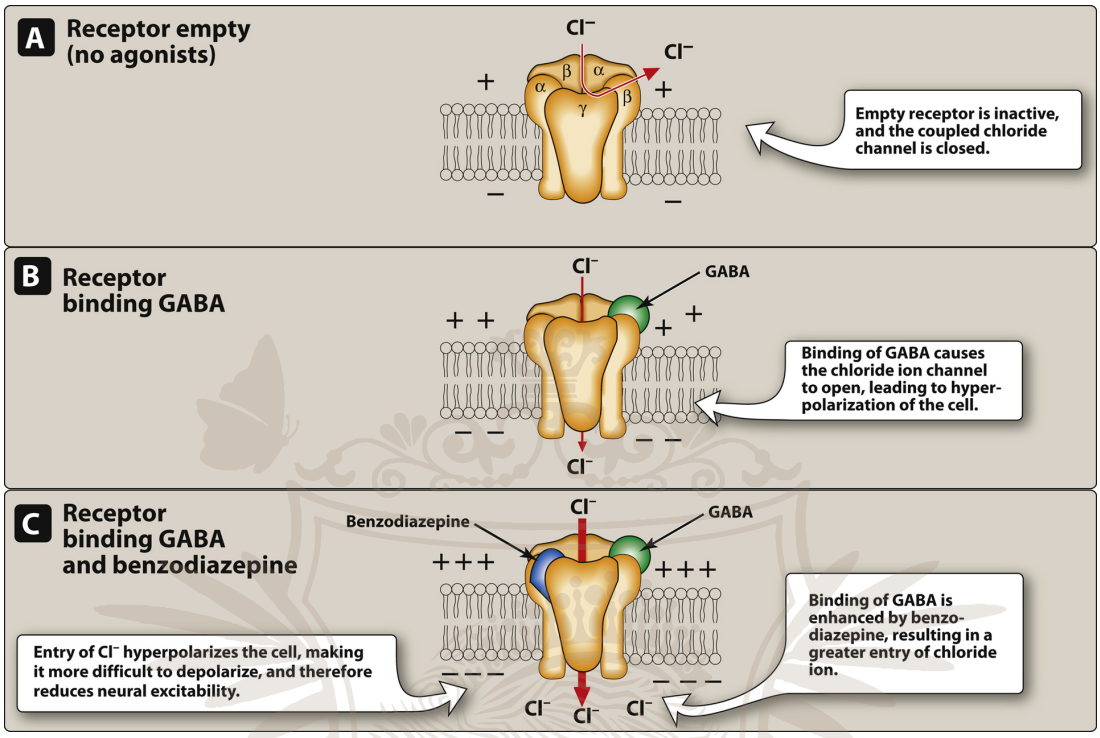

Figure 16.3 Schematic diagram of benzodiazepine–GABA–chloride ion channel complex.GABA = γ-aminobutyric acid.

B. Actions

All benzodiazepines exhibit the following actions to some extent:

1. **Reduction of anxiety:** At low doses, the benzodiazepines are anxiolytic. They are thought to reduce anxiety by selectively enhancing GABAergic transmission in neurons having the α_2 subunit in their $GABA_A$ receptors, thereby inhibiting neuronal circuits in the limbic system of the brain.

2. **Sedative/Hypnotic:** All benzodiazepines have sedative and calming properties, and some can produce hypnosis (artificially produced sleep) at higher doses. The hypnotic effects are mediated by the α_1-$GABA_A$ receptors.

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3.Anterograde amnesia: Temporary impairment of memory with the use of the benzodiazepines is also mediated by the α_1-$GABA_A$ receptors. The ability to learn and form new memories is also impaired.

4.Anticonvulsant: This effect is partially, although not completely, mediated by α_1-$GABA_A$ receptors.

5.Muscle relaxant: At high doses, the benzodiazepines relax the spasticity of skeletal muscle, probably by increasing presynaptic inhibition in the spinal cord, where the α_2-$GABA_A$ receptors are largely located. [Note: *Baclofen* [BAK-loe-fen] is a muscle relaxant that is believed to affect GABA receptors at the level of the spinal cord.]

C. Therapeutic uses

The individual benzodiazepines show small differences in their relative anxiolytic, anticonvulsant, and sedative properties. However, pharmacokinetic considerations are often important in the selection of a benzodiazepine agent.

1.Anxiety disorders: Benzodiazepines are effective for the treatment of anxiety associated with panic disorder, generalized anxiety disorder, social anxiety disorder, performance anxiety, and extreme phobias, such as fear of flying. The benzodiazepines are also useful in treating anxiety related to depression and schizophrenia. These drugs should be reserved for severe anxiety and should not be used to manage the stress of everyday life. Because of their addictive potential, they should only be used for short periods of time. The longer-acting agents, such as *clonazepam* [kloe-NAZ-e-pam], *lorazepam* [lor-AZ-e-pam], and *diazepam* [dye-AZ-e-pam], are often preferred in patients with anxiety that require prolonged treatment. The anxiolytic effects of the benzodiazepines are less subject to tolerance than the sedative and hypnotic effects. [Note: Tolerance is decreased

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responsiveness to repeated doses of the drug that occurs when used for more than 1 to 2 weeks.] For panic disorders, *alprazolam* [al-PRAY-zoe-lam] is effective for short- and long-term treatment, although it may cause withdrawal reactions in approximately 30% of patients.

2.Sleep disorders: Benzodiazepine hypnotics decrease sleep onset latency (the amount of time it takes to fall asleep) and increase stage II of non-rapid eye movement (NREM) sleep. Both rapid eye movement (REM) sleep and slow-wave sleep are decreased. In the treatment of insomnia, it is important to balance the sedative effect needed at bedtime with the residual sedation ("hangover") that may occur upon awakening. In general, short-acting agents with a rapid onset of action (for example, *triazolam* [try-AY-zoe-lam]) are effective in treating individuals who have problems falling asleep, and intermediate-acting (for example, *temazepam* [te-MAZ-e-pam]) or long-acting agents are useful for patients who experience frequent awakenings or have difficulty staying asleep. The risk of withdrawal and rebound insomnia after discontinuation is higher with shorter-acting agents such as *triazolam*, while the possibility of daytime sedation ("hangover") is much greater with longer-acting agents. For example, long-acting *flurazepam* [flure-AZ-e-pam] is rarely used, due to its extended half-life, which may result in excessive daytime sedation and accumulation of the drug, especially in the elderly. *Estazolam* [eh-STAY-zoe-lam] and *quazepam* [QUAY-ze-pam] are considered intermediate- and long-acting hypnotic agents, respectively. In most cases, hypnotics should be used for only a limited time, usually 1 to 3 weeks.

3.Amnesia: The shorter-acting agents are often employed as premedication for anxiety-provoking surgeries and procedures. These agents cause a form of conscious sedation, allowing the patient to be receptive to instructions and follow commands during the procedure. *Midazolam* [mi-

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DAY-zoe-lam] is the most commonly used benzodiazepine to provide this level of sedation, and its use frequently results in anterograde amnesia that renders the patient without memory of the event. Deeper levels of sedation occur with escalating doses of benzodiazepines, and in higher doses these agents are able to produce a state of general anesthesia.

4.Seizures: *Clonazepam* is occasionally used as an adjunctive therapy for certain types of seizures, whereas *lorazepam* and *diazepam* are the drugs of choice in terminating status epilepticus (see Chapter 19). Due to cross-tolerance, *chlordiazepoxide* [klor-di-az-e-POX-ide], *clorazepate* [klor-AZ-e-pate], *diazepam*, *lorazepam*, and *oxazepam* [ox-AZ-e-pam] are useful in the acute treatment of alcohol withdrawal and reduce the risk of withdrawal-related seizures.

5.Muscular disorders: *Diazepam* is useful in the treatment of skeletal muscle spasms and in treating spasticity from degenerative disorders, such as multiple sclerosis and cerebral palsy.

D. Pharmacokinetics

1.Absorption and distribution: The benzodiazepines are lipophilic. They are rapidly and completely absorbed after oral administration, distribute throughout the body (large volume of distribution), and penetrate into the CNS.

2.Duration of action: The half-lives of the benzodiazepines are important clinically, because the duration of action may determine their therapeutic usefulness. The benzodiazepines can be roughly divided into short-, intermediate-, and long-acting groups (Figure 16.4). The longer-acting agents form active metabolites with long half-lives. However, with some benzodiazepines, the clinical duration of action does not correlate with the actual half-life (otherwise, a dose of *diazepam* could conceivably be given

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only every other day, given its long half-life and active metabolites). This may be due to receptor dissociation rates in the CNS and subsequent redistribution to fatty tissues and other areas.

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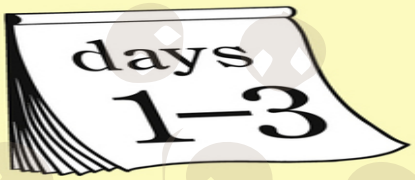
DURATION OF ACTION OF BENZODIAZEPINES

Long-acting



Chlordiazepoxide
Flurazepam
Quazepam

Intermediate-acting

10–20 Hours

Clonazepam
Clorazepate
Diazepam
Estazolam
Lorazepam
Oxazepam
Temazepam

Short-acting

3–8 Hours

Alprazolam
Midazolam
Triazolam

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Figure 16.4 Comparison of the durations of action of the benzodiazepines.

3.Metabolism and elimination: Most benzodiazepines, including *chlordiazepoxide* and *diazepam*, are metabolized by the hepatic microsomal system to compounds that are also active. [Note: Many of these agents are metabolized by CYP3A4 and are subject to numerous drug interactions.] For these benzodiazepines, the apparent half-life of the drug represents the combined actions of the parent drug and its metabolites. The benzodiazepines are excreted in the urine as glucuronides or oxidized metabolites. [Note: *Lorazepam*, *oxazepam*, and *temazepam* do not undergo phase I metabolism. They are glucuronidated to inactive metabolites. Because these agents have no active metabolites, they are less prone to accumulation and drug interactions, and they are useful in patients with renal or hepatic dysfunction.] All benzodiazepines cross the placenta and may depress the CNS of the newborn if given before birth. The benzodiazepines are not recommended for use during pregnancy. Nursing infants may also be exposed to the drugs in breast milk.

E. Dependence

Psychological and physical dependence can develop if high doses of benzodiazepines are given for a prolonged period. All benzodiazepines are controlled substances. Abrupt discontinuation of these agents results in withdrawal symptoms, including confusion, anxiety, agitation, restlessness, insomnia, tension, and (rarely) seizures. Benzodiazepines with a short elimination half-life, such as *triazolam,* induce more abrupt and severe withdrawal reactions than those seen with drugs that are slowly eliminated such as *flurazepam* (Figure 16.5). Withdrawal reactions and rebound anxiety or insomnia, and return of panic

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symptoms, are common following discontinuation of *alprazolam*, even when the drug is tapered.

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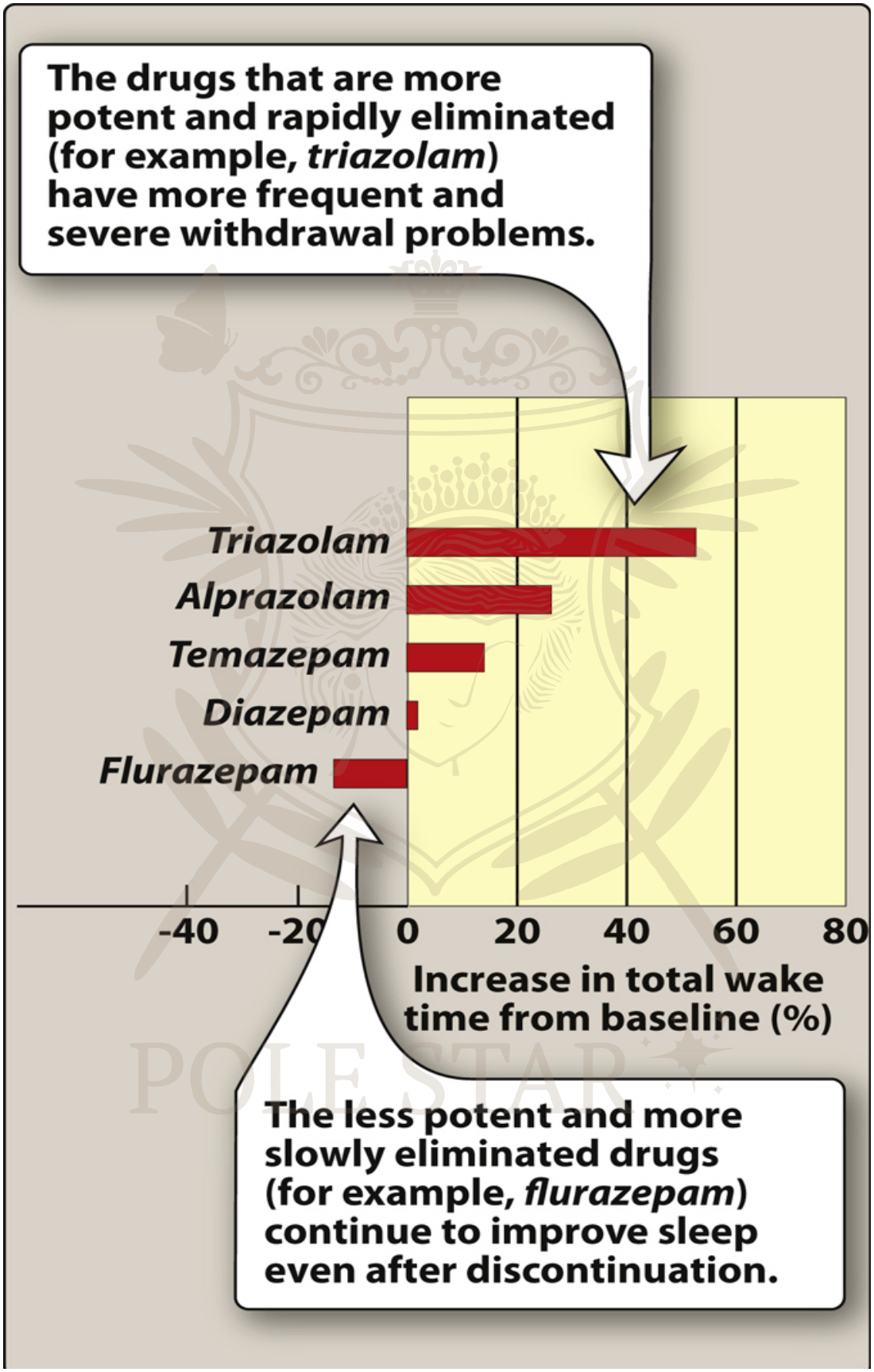
The drugs that are more potent and rapidly eliminated (for example, *triazolam*) have more frequent and severe withdrawal problems.
Triazolam
Alprazolam
Temazepam
Diazepam
Flurazepam
-40
-20
0
20
40
60
80
Increase in total wake time from baseline (%)
The less potent and more slowly eliminated drugs (for example, *flurazepam*) continue to improve sleep even after discontinuation.

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Figure 16.5 Frequency of rebound insomnia resulting from discontinuation of benzodiazepine therapy.Data from A.Kales . Excertpa Medical Congress Series. 899: 149 (1989).

F. Adverse effects

Drowsiness and confusion are the most common adverse effects of the benzodiazepines. Ataxia occurs at high doses and precludes activities that require fine motor coordination, such as driving an automobile. Cognitive impairment (decreased recall and retention of new knowledge) can occur with use of benzodiazepines. Benzodiazepines should be used cautiously in patients with liver disease. Alcohol and other CNS depressants enhance the sedative–hypnotic effects of the benzodiazepines. Concurrent use of benzodiazepines and opioids should be avoided due to the risk of profound sedation and respiratory depression, which can lead to coma or death. Benzodiazepines are, however, considerably less dangerous than the older anxiolytic and hypnotic drugs, such as barbiturates. As a result, a drug overdose is seldom lethal unless other central depressants, such as alcohol or opioids, are taken concurrently.

III. BENZODIAZEPINE ANTAGONIST

Flumazenil [floo-MAZ-eh-nill] is a GABA receptor antagonist that rapidly reverses the effects of benzodiazepines in cases of overdose or toxicity. The drug is available for intravenous (IV) administration only. Onset is rapid, but the duration is short, with a half-life of about 1 hour. Frequent administration may be necessary to maintain reversal following overdose of a long-acting benzodiazepine. Administration of *flumazenil* may precipitate withdrawal in dependent patients or cause seizures if a benzodiazepine is used to control seizure activity. Seizures may also result if the patient has a mixed ingestion with tricyclic antidepressants or antipsychotics. Dizziness,

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nausea, vomiting, and agitation are the most common adverse effects.

IV. OTHER ANXIOLYTIC AGENTS

A. Antidepressants

Many antidepressants are effective in the treatment of chronic anxiety disorders and should be considered as first-line agents, especially in patients with concerns for addiction or dependence. Selective serotonin reuptake inhibitors (SSRIs, such as *escitalopram* or *paroxetine*) or serotonin–norepinephrine reuptake inhibitors (SNRIs, such as *venlafaxine* or *duloxetine*) may be used alone or prescribed in combination with a benzodiazepine during the first week of treatment (Figure 16.6). After 4 to 6 weeks, when the antidepressant begins to produce an anxiolytic effect, the benzodiazepine dose can be tapered. While only certain SSRIs or SNRIs have been approved for the treatment of anxiety disorders such as generalized anxiety disorder (GAD), the efficacy of these drugs is most likely a class effect. Long-term use of antidepressants and benzodiazepines for anxiety disorders is often required to maintain ongoing benefit and prevent relapse.

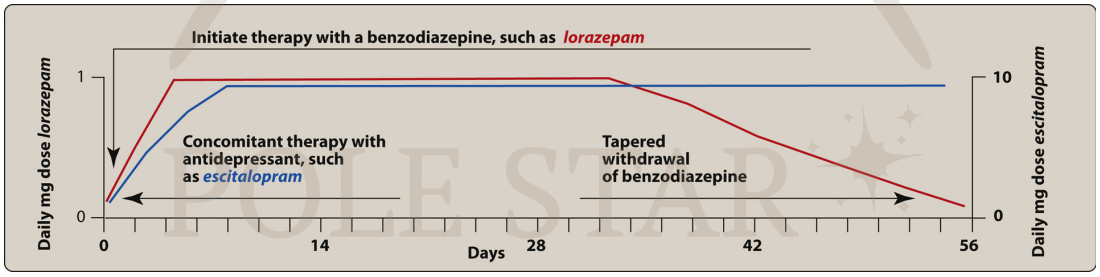

Figure 16.6 Treatment guideline for persistent anxiety.Data from E. C.Dimitrion , A. J.Parashos , and J. S.Giouzepas . *Drug Invest*. 4: 316 (1992).

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B. Buspirone

Buspirone [byoo-SPYE-rone] is useful for the chronic treatment of GAD and has an efficacy comparable with that of benzodiazepines. It has a slow onset of action and is not effective for short-term or "as-needed" treatment of acute anxiety. The actions of *buspirone* appear to be mediated by serotonin ($5\text{-}HT_{1A}$) receptors, although it also displays some affinity for D_2 dopamine receptors and $5\text{-}HT_{2A}$ serotonin receptors. Thus, its mode of action differs from that of the benzodiazepines. In addition, *buspirone* lacks the anticonvulsant and muscle-relaxant properties of the benzodiazepines. The frequency of adverse effects is low, with the most common effects being headache, dizziness, nervousness, nausea, and light-headedness. Sedation and psychomotor and cognitive dysfunction are minimal, and dependence is unlikely. *Buspirone* does not potentiate the CNS depression of alcohol. Figure 16.7 compares common adverse effects of *buspirone* and the benzodiazepine *alprazolam*.

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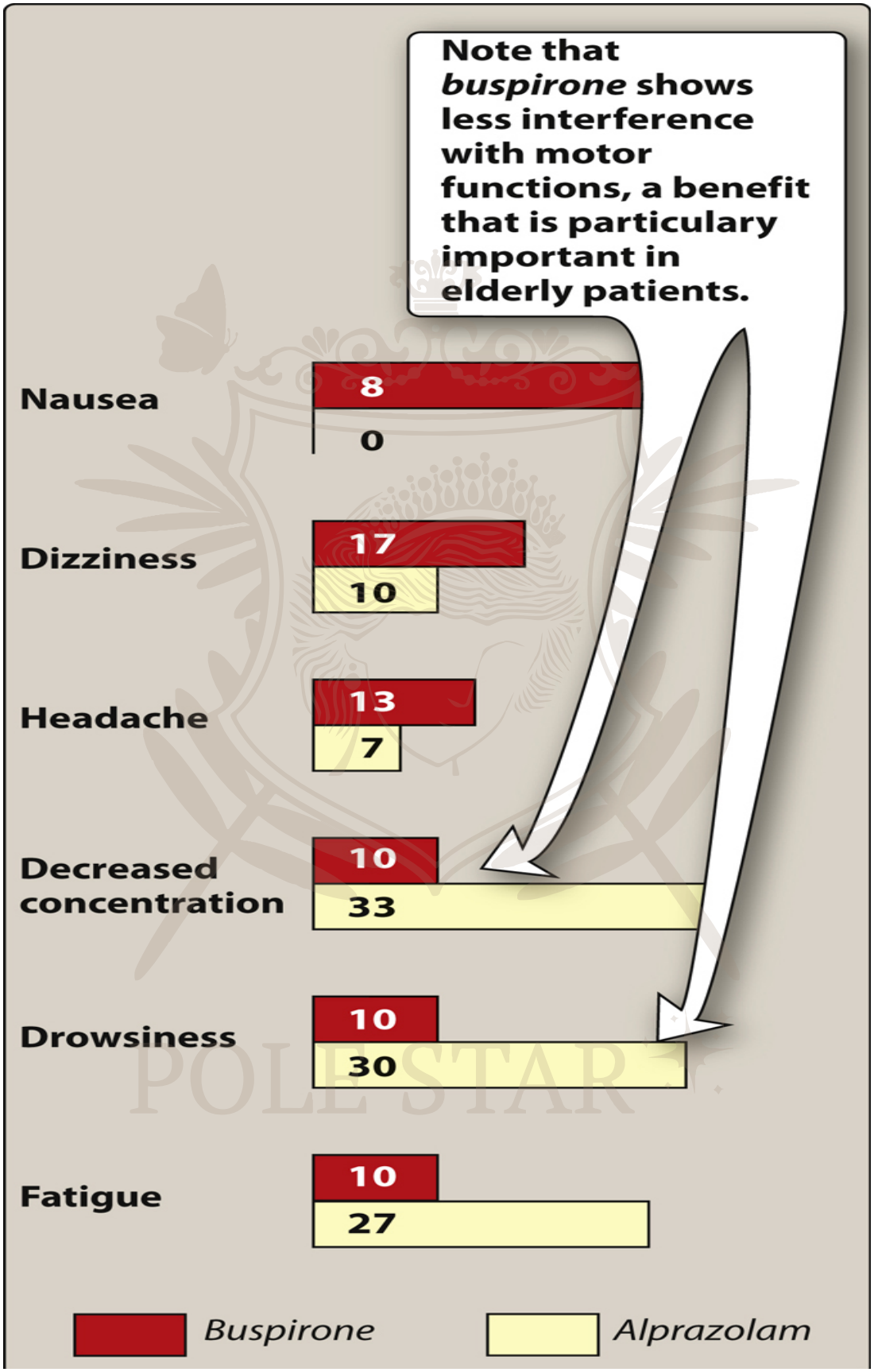
Note that *buspirone* shows less interference with motor functions, a benefit that is particulary important in elderly patients.
Nausea
8
0
Dizziness
17
10
Headache
13
7
Decreased concentration
10
33
Drowsiness
10
30
Fatigue
10
27
Buspirone
Alprazolam

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Figure 16.7 Comparison of common adverse effects of *buspirone* and *alprazolam*.Results are expressed as the percentage of patients showing each symptom.

Clinical Application 16.1: Management of Generalized Anxiety Disorder (GAD)

GAD is a condition characterized by persistent and excessive anxiety or worrying that occurs on most days for at least 6 months. Patients with GAD may experience functional impairment, as well as physical symptoms such as muscle tension, fatigue, and sleep problems. Management of GAD includes psychotherapy (cognitive behavioral therapy) and/or medications. Benzodiazepines (for example, *alprazolam*, *lorazepam*) may be used for acute relief of anxiety symptoms. However, for patients who require drug therapy for management of chronic anxiety, SSRIs, such as *escitalopram* or *paroxetine*, or SNRIs antidepressants such as *venlafaxine* or *duloxetine* are considered first-line therapy (see Chapter 17). The SSRIs and SNRIs have the advantage of being able to treat other comorbid psychiatric conditions such as depression and panic disorder, without the concerns of dependency and potential for abuse associated with benzodiazepines. *Buspirone* is an alternative agent for the management of GAD. For patients who do not achieve a full response with an adequate dose of SSRIs or SNRIs, switch to another SSRI or SNRI agent, or addition of benzodiazepines, buspirone, or atypical antipsychotics can be considered.

V. BARBITURATES

The barbiturates were formerly the mainstay of treatment to sedate patients or to induce and maintain sleep. With the exception of a few special therapeutic uses, they have been largely replaced by the benzodiazepines, primarily because barbiturates induce tolerance and physical dependence, are lethal in overdose, and are associated with severe withdrawal symptoms. All barbiturates are controlled substances and have the potential for abuse.

A. Mechanism of action

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The sedative–hypnotic action of the barbiturates is due to their interaction with $GABA_A$ receptors, which enhances GABAergic transmission. The binding site of barbiturates on the GABA receptor is distinct from that of the benzodiazepines. Barbiturates potentiate GABA action on chloride entry into the neuron by prolonging the duration of the chloride channel openings. In addition, barbiturates may inhibit release of the excitatory neurotransmitter glutamate and block glutamate receptors. These molecular actions lead to decreased neuronal activity.

B. Actions

Barbiturates are classified according to their duration of action (Figure 16.8). Long-acting *phenobarbital* [fee-noe-BAR-bi-tal] has a duration of action greater than a day. *Pentobarbital* [pen-toe-BAR-bi-tal], *secobarbital* [see-koe-BAR-bi-tal], *amobarbital* [am-oh-BAR-bi-tal], and *butalbital* [bu-TAL-bi-tal] are short-acting barbiturates.

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DURATION OF ACTION OF BARBITURATES

Long-acting

Phenobarbital

Short-acting

3–8 Hours

Pentobarbital
Secobarbital
Amobarbital

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Figure 16.8 Barbiturates classified according to their durations of action.

1. Depression of CNS: At low doses, the barbiturates produce sedation (have a calming effect and reduce excitement). At higher doses, the drugs cause hypnosis, followed by anesthesia (loss of feeling or sensation), and, finally, coma and death. Thus, any degree of depression of the CNS is possible, depending on the dose. Barbiturates do not raise the pain threshold and have no analgesic properties. They may even exacerbate pain. Chronic use leads to tolerance.

2. Respiratory depression: Barbiturates suppress the hypoxic and chemoreceptor response to CO_2, and overdose is followed by respiratory depression and death.

C. Therapeutic uses

1. Anesthesia: The ultra–short-acting barbiturates such as *methohexital* [METH-oh-HEX-i-tal] are used intravenously to induce anesthesia for short surgeries or procedures. *Methohexital* is particularly useful for electroconvulsive (ECT) therapy because it lowers the seizure threshold requisite for successful ECT therapy. [Note: ECT is a treatment for refractory major depression. It involves electrical stimulation of the brain to induce brief seizure activity.] Intravenous *pentobarbital* may be used to induce a "barbiturate coma" in patients with traumatic brain injury and elevated intracranial pressure who are unresponsive to other therapies.

2. Anticonvulsant: *Phenobarbital* has specific anticonvulsant activity that is distinguished from the nonspecific CNS depression caused by other barbiturates. However, *phenobarbital* can depress cognitive development in children and decrease cognitive performance in adults, and it should be used for management of epilepsy only if other

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therapies have failed. Similarly, *phenobarbital* may be used for the treatment of refractory status epilepticus.

3.Sedative/Hypnotic: Barbiturates have been used as mild sedatives to relieve anxiety, nervous tension, and insomnia. When used as hypnotics for the treatment of insomnia, they suppress REM sleep more than other stages of sleep. However, the use of barbiturates for insomnia is no longer generally accepted, given their adverse effects and potential for tolerance. *Butalbital* is commonly used in combination products (with *acetaminophen* and *caffeine* or *aspirin* and *caffeine*) as a sedative to assist in the management of tension or migraine headaches.

D. Pharmacokinetics

Barbiturates are well absorbed after oral administration, distribute throughout the body (large volume of distribution), and penetrate the blood–brain barrier. All barbiturates redistribute from the brain to the splanchnic areas, to skeletal muscle, and, finally, to adipose tissue. Barbiturates readily cross the placenta and can cause respiratory depression in newborns if administered around the time of delivery. These agents are metabolized in the liver, and inactive metabolites are excreted in urine.

E. Adverse effects

Barbiturates cause drowsiness, impaired concentration, and mental and psychomotor impairment (Figure 16.9). The CNS depressant effects of barbiturates synergize with those of *ethanol*.

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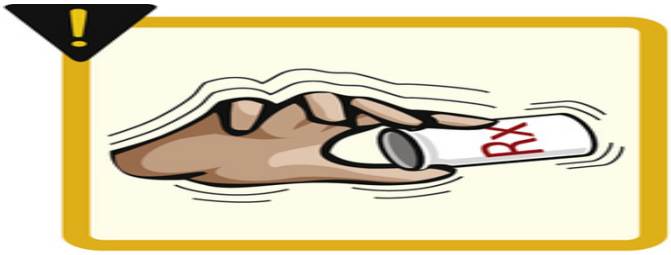
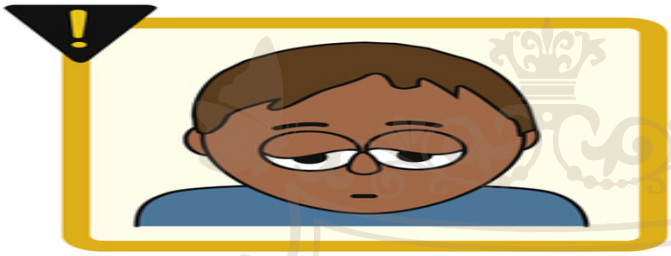
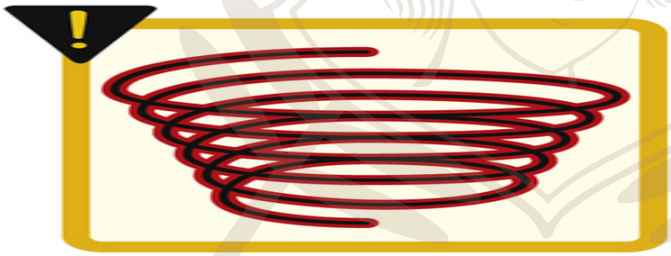


Potential for addiction



Drowsiness

Nausea



Vertigo

Tremors

Enzyme induction

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Figure 16.9 Adverse effects of barbiturates.

Hypnotic doses of barbiturates produce a drug "hangover" that may lead to impaired ability to function normally for many hours after waking. Occasionally, nausea and dizziness occur. Barbiturates induce cytochrome P450 (CYP450) microsomal enzymes in the liver. Therefore, chronic barbiturate administration diminishes the action of many drugs that are metabolized by the CYP450 system. Barbiturates are contraindicated in patients with acute intermittent porphyria, since they can induce enzymes involved in the production of porphyrin. Abrupt withdrawal from barbiturates may cause tremors, anxiety, weakness, restlessness, nausea and vomiting, seizures, delirium, and cardiac arrest. Withdrawal is much more severe than that associated with opioids and can result in death. Death may also result from overdose secondary to apnea or cardiovascular collapse. No reversal agent exists, and treatment includes supportive care and gastric decontamination for recent ingestions.

VI. OTHER HYPNOTIC AGENTS

A. Zolpidem

The hypnotic *zolpidem* [ZOL-pi-dem] is not structurally related to benzodiazepines, but it binds to $GABA_A$ receptors with relative selectivity for the benzodiazepine site with the α_1 subunit. *Zolpidem* has no anticonvulsant or muscle-relaxing properties at hypnotic doses. It shows few withdrawal effects, exhibits minimal rebound insomnia, and little tolerance occurs with prolonged use. *Zolpidem* is rapidly absorbed after oral administration. It has a rapid onset of action and short elimination half-life (about 2-3 hours). The drug provides a hypnotic effect for approximately 5 hours (Figure 16.10). [Note: A lingual spray and an extended-release formulation are also available. A sublingual tablet

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formulation may be used for middle-of-the-night awakening.] *Zolpidem* undergoes hepatic oxidation by the CYP450 system to inactive products. Thus, drugs such as *rifampin*, which induce this enzyme system, shorten the half-life of *zolpidem*, and drugs that inhibit the CYP3A4 isoenzyme may increase the half-life. Adverse effects of *zolpidem* include headache, dizziness, anterograde amnesia, and next-morning impairment (especially with extended-release formulations). Complex sleep behaviors such as sleep-walking, sleep-driving, and performing other activities while not fully awake have been reported and are a warning for this class of medications. Unlike the benzodiazepines, at usual hypnotic doses, the nonbenzodiazepine drugs, *zolpidem*, *zaleplon*, and *eszopiclone*, do not significantly alter the various sleep stages and, hence, are often the preferred hypnotics. All three agents are controlled substances with warnings for dependency. In case of overdose, the sedative effects of *zolpidem* and *eszopiclone* can be reversed with the benzodiazepine antagonist *flumazenil*.

POLE STAR

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Figure 16.10 Onset and duration of action of the commonly used nonbenzodiazepine hypnotic agents.

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B. Zaleplon

Zaleplon [ZAL-e-plon] is an oral nonbenzodiazepine hypnotic similar to *zolpidem*; however, *zaleplon* causes fewer residual effects on psychomotor and cognitive function compared with *zolpidem* or the benzodiazepines. This may be due to its rapid elimination, with a half-life of approximately 1 hour. Because of its quick onset of action and short half-life, the drug is best used for patients who have difficulty falling asleep. *Zaleplon* is metabolized by CYP3A4.

C. Eszopiclone

Eszopiclone [es-ZOE-pi-clone] is an oral nonbenzodiazepine hypnotic that has been shown to be effective for insomnia for up to 6 months. *Eszopiclone* is rapidly absorbed (time to peak, 1 hour), extensively metabolized by oxidation and demethylation via the CYP450 system, and mainly excreted in urine. Elimination half-life is approximately 6 hours. Adverse events with *eszopiclone* include anxiety, dry mouth, headache, peripheral edema, somnolence, and unpleasant taste.

D. Melatonin receptor agonists

Ramelteon [ram-EL-tee-on] and *tasimelteon* [taz-ee-MEL-tee-on] are selective agonists at the MT_1 and MT_2 subtypes of melatonin receptors. Melatonin is a hormone secreted by the pineal gland that helps to maintain the circadian rhythm underlying the normal sleep–wake cycle. Stimulation of MT_1 and MT_2 receptors by *ramelteon* and *tasimelteon* is thought to induce and promote sleep. These agents have minimal potential for abuse, and no evidence of dependence or withdrawal has been observed. Therefore, *ramelteon* and *tasimelteon* can be administered long-term. *Ramelteon* is indicated for the treatment of insomnia characterized by difficulty falling asleep (increased sleep latency). Common adverse effects of *ramelteon* include dizziness, fatigue, and somnolence. *Ramelteon* may also increase prolactin levels.

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Tasimelteon is indicated for non–24-hour sleep–wake disorder, often experienced by patients who are blind. The most common adverse effects of *tasimelteon* are headache, abnormal dreams, increase in liver function tests, and possible upper respiratory tract infections. CYP1A2 and CYP3A4 are the principal isoenzymes required for metabolism of *ramelteon* and *tasimelteon*, and, thus, drug–drug interactions are possible with inducers or inhibitors of these enzymes.

E. Antihistamines

Antihistamines with sedating properties, such as *diphenhydramine*, *hydroxyzine*, and *doxylamine*, are effective in treating mild situational insomnia (see Chapter 39). However, they have undesirable adverse effects (such as anticholinergic effects) that make them less useful than the benzodiazepines and the nonbenzodiazepines. Sedative antihistamines are marketed in numerous over-the-counter products.

F. Antidepressants

The use of sedating antidepressants with strong antihistamine profiles has been ongoing for decades. *Doxepin* [DOX-e-pin], an older tricyclic agent with SNRI mechanisms of antidepressant and anxiolytic action, is approved at low doses for the management of insomnia. Other antidepressants, such as *trazodone* [TRAZ-oh-done], *mirtazapine* [mir-TAZ-a-pine], and older tricyclic antidepressants with strong antihistamine properties are used off-label for the treatment of insomnia (see Chapter 17).

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Clinical Application 16.2: Management of Insomnia

Patients with insomnia experience difficulty falling asleep or staying asleep. Both short-term insomnia (insomnia for less than 3 months, usually due to an acute life stressor such as a death in the family, divorce, or other major life change) and chronic insomnia benefit from employing principles of sleep hygiene and stress management. Many agents are available to manage transient or short-term insomnia (for example, nonbenzodiazepines, benzodiazepines, and antihistamines); however, these agents do not have long-

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term data for efficacy despite their continued use in the practice setting. If a patient demonstrates symptoms of chronic insomnia, a medical and psychiatric evaluation should be performed to determine if an underlying issue is contributing to the insomnia. Examples of chronic conditions that can contribute to insomnia include pulmonary disease, sleep apnea, heart failure, chronic pain, substance use disorders, and other psychiatric conditions, such as anxiety and depression. When medications are selected for the treatment of insomnia, the clinician should consider the agent's risk for abuse and dependency, especially in patients with a history of drug abuse, and, thus, should select a treatment without a risk for abuse or dependence. The nonbenzodiazepine hypnotic agents still utilize the benzodiazepine receptor for their mechanism of action and, thus, are controlled substances with risks for anterograde amnesia, disinhibition, abuse, and dependence. These agents are widely used in current society and have largely replaced the benzodiazepines for the management of short-term insomnia; however, their risks are similar.

G. Orexin receptor antagonists

Suvorexant [soo-voe-REX-ant] and *lemborexant* [lem-boe-REX-ant] are antagonists of the orexin receptors OX1R and OX2R. Orexin is a neuropeptide that promotes wakefulness. Antagonism of the effects of orexin is thought to suppress the wake drive from this neuropeptide. This antagonism may also explain the adverse events that are similar to signs of narcolepsy, such as sleep paralysis, cataplexy, and hypnogogic or hypnopompic hallucinations. The loss of orexin-producing neurons is believed to be an underlying pathology for narcolepsy. Daytime somnolence and increased suicidal ideation are other reported adverse effects. *Suvorexant* and *lemborexant* are mainly metabolized by CYP3A4 and, thus, may have drug interactions with CYP3A4 inducers or inhibitors.

Figure 16.11 summarizes the therapeutic disadvantages and advantages of some of the anxiolytic and hypnotic drugs.

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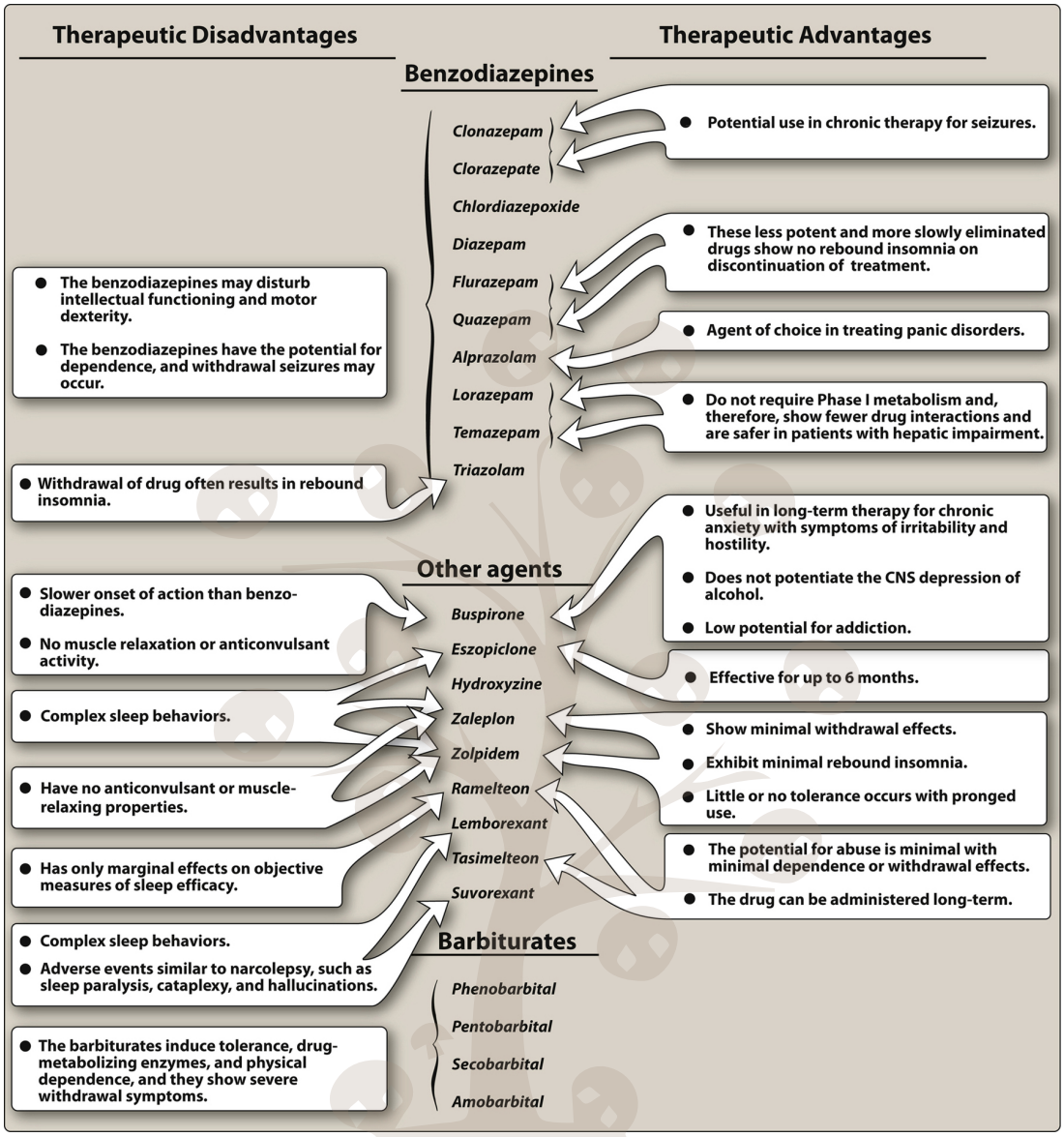

Figure 16.11 Therapeutic disadvantages and advantages of some anxiolytic and hypnotic agents.CNS = central nervous system.

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Chapter Summary

- Anxiolytics and hypnotic medications generally have CNS depressant qualities, and these agents should be used under clinical supervision for the shortest amount of time possible.
- The enhancement of GABA activity by binding to the benzodiazepine receptor provides the benzodiazepines (for example, *alprazolam*) and the

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nonbenzodiazepines (for example, *zolpidem*) a rapid onset of effect.
- For the short-term and rapid management of anxiety, the benzodiazepines are effective and demonstrate their efficacy within hours to days.
- For the long-term management of anxiety disorders, medications with a low risk for abuse or dependence should be considered, such as SSRIs or SNRIs, instead of benzodiazepines, if possible.
- Hypnotic agents for the management of insomnia should be used for the shortest amount of time possible, and noncontrolled substances reduce the risk for dependency, such as the agents with antihistamine properties (for example, *doxepin*).
- Chronic insomnia often has an underlying pathology, such as sleep apnea, that maintains the symptoms of insomnia and daytime fatigue, and the use of hypnotics may have limitations in efficacy when used long-term without addressing these underlying pathologies.

STUDY QUESTIONS

Choose the ONE best answer.

16.1 Which of the following statements is correct regarding benzodiazepines?

A. Benzodiazepines directly open chloride channels.
B. Benzodiazepines show analgesic actions.
C. Clinical improvement of anxiety requires 2 to 4 weeks of treatment with benzodiazepines.
D. All benzodiazepines have some sedative effects.

Correct answer = D. Although all benzodiazepines can cause sedation, the drugs labeled "benzodiazepines" in Figure 16.1 are promoted for the treatment of sleep disorder. Benzodiazepines enhance the binding of GABA to $GABA_A$ receptors, which increases the permeability of chloride; however, benzodiazepines do not open chloride channels independent of GABA. The benzodiazepines do not relieve pain but may reduce the anxiety associated with pain. Unlike the tricyclic antidepressants and the monoamine oxidase inhibitors, the benzodiazepines are effective within hours of administration.

16.2 Which one of the following is a short-acting hypnotic?

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A. Flurazepam
B. Diazepam
C. Chlordiazepoxide
D. Triazolam

Correct answer = D. Triazolam is a short-acting hypnotic agent with the shortest half-life. It is best used for treatment of insomnia. It causes little daytime sedation. The other medications listed are longer acting with longer half-lives.

16.3 A 36-year-old man reports difficulty falling asleep for the past 2 weeks but needs to be able to wake up early in the morning for work and does not want any daytime sedation. Which of the following medications is best to recommend for the treatment of his insomnia?

A. Quazepam
B. Flurazepam
C. Zaleplon
D. Buspirone

Correct answer = C. Zaleplon has the shortest half-life and duration of action of this group. Buspirone is not effective as a hypnotic agent. Quazepam and flurazepam have a longer duration of action. These agents reduce nighttime awakenings but have a greater risk of daytime sedation or hangover effect compared with zaleplon.

16.4 A 45-year-old woman reports constant daytime anxiety about work and family problems. This is causing difficulties functioning and participating in necessary daily activities. Which of the following agents has a rapid anxiolytic effect and is best for the acute management of her anxiety?

A. Buspirone
B. Venlafaxine
C. Alprazolam
D. Sertraline

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Correct answer = C. The benzodiazepines have same-day, first-dose efficacy for anxiety, whereas the other agents require 2 to 8 weeks for clinically significant improvement in anxiety to occur.

16.5 A 75-year-old woman is demonstrating signs and symptoms of insomnia, especially difficulty falling asleep. She is afraid of taking a medication that can negatively affect her memory and concentration, as she is still working as a bookkeeper. She has been taking temazepam for the past 4 days and has noticed a memory problem and would like to discontinue this medication. Which medication is most appropriate to treat the insomnia with a lower risk for cognitive impairment?

A. Diphenhydramine
B. Zolpidem
C. Lemborexant
D. Ramelteon

Correct answer = D. All of these agents have been associated with cognitive impairments, including possible memory impairment. Diphenhydramine likely causes its cognitive problems from its anticholinergic and antihistaminergic effects. Zolpidem is a well-known cause of cognitive impairment, including anterograde amnesia. Lemborexant has been reported to have CNS impairment, including impairment of daytime wakefulness. Ramelteon is a noncontrolled hypnotic agent acting as a melatonin receptor agonist. It is considered to have a lower risk for cognitive impairment compared with the other agents listed but is not without any risk for cognitive impairment.

16.6 An 18-year-old woman is admitted to the emergency room after an accidental overdose of alprazolam. She is unconscious and not considered a regular user of any medications or illicit drugs. Which of the following treatments could be used to reverse the effect of the alprazolam overdose?

A. Lorazepam
B. Ramelteon
C. Flumazenil

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D. Naloxone

Correct answer = C. Flumazenil is indicated to reverse the effects of benzodiazepines via antagonism of the benzodiazepine receptor. It may also be used to reverse effects of zolpidem and eszopiclone. It should be used with caution because of a risk of seizures if the patient has been a long-time recipient of benzodiazepines or if the overdose attempt was with mixed drugs. Naloxone is an opioid receptor antagonist. The other agents are not efficacious in reversing effects of benzodiazepines.

16.7A patient is taking fluvoxamine for obsessive compulsive disorder and requires a medication for insomnia. Which of the following agents is the best choice for this patient due to having the lowest risk for drug–drug interactions with fluvoxamine?

A. Triazolam
B. Ramelteon
C. Temazepam
D. Doxepin

Correct answer = C. The SSRIs such as fluvoxamine are the drugs of choice for obsessive compulsive disorder; however, fluvoxamine is a moderate to strong inhibitor of the CYP1A2 and the CYP3A4 isoenzymes, which are required to metabolize triazolam, ramelteon, and doxepin. Temazepam undergoes phase two conjugation for its metabolism and does not require the CYP450 enzymes for its elimination.

16.8A 40-year-old man with a 25-year history of generalized anxiety disorder and a 10-year history of alcohol use disorder (he has been clean and sober for 5 years) presents to the clinic complaining of significant and continuous anxiety. The patient is currently on no medication and reports minimal improvement with psychotherapy. Which of the following anxiolytics would be the best choice to prescribe for long-term use?

A. Venlafaxine
B. Clonazepam

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C. Alprazolam
D. Chlordiazepoxide

Correct answer = A. Given the history of alcohol use disorder, the SNRI venlafaxine is the best choice to manage this patient's GAD. All of the other choices are benzodiazepines, which are controlled substances with a risk for dependency and abuse.

16.9 Which of the following hypnotic agents is most likely to cause cataplexy and sleep paralysis as adverse reactions?

A. Doxepin
B. Ramelteon
C. Temazepam
D. Suvorexant

Correct answer = D. Possibly due to its orexin receptor antagonism, suvorexant has been reported more than the other agents to cause adverse reactions such as cataplexy, sleep paralysis, and hallucinations upon going to sleep (hypnogogic) or upon wakening (hypnopompic). The other agents may still cause complex sleep behaviors but are not associated with those listed for suvorexant or lemborexant.

16.10 Which of the following agents is commonly used as an anxiolytic for diagnostic procedures such as endoscopy or as a preanesthetic sedative due to its short half-life and high potency?

A. Clonazepam
B. Midazolam
C. Ramelteon
D. Lemborexant

Correct answer = B. Midazolam is commonly used for rapid anxiolysis and sedation for patients undergoing unpleasant and anxiety-provoking procedures. Its very short half-life, availability as an injection, and short duration of effect are conducive for brief interventions and procedures. Its effect of anterograde amnesia is sometimes a benefit for patients to avoid a negative memory of the

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unpleasant procedure. Clonazepam is only available orally and has a much longer half-life and duration of effect. Ramelteon and lemborexant do not have applications as preanesthetics and have not been approved for such use.

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17

Antidepressants

Jose A. Rey

I. OVERVIEW

The symptoms of depression include feelings of sadness and hopelessness, as well as the inability to experience pleasure in usual activities, changes in sleep patterns and appetite, loss of energy, and suicidal thoughts. Mania is characterized by the opposite behavior: enthusiasm, anger, rapid thought and speech patterns, extreme self-confidence, and impaired judgment. This chapter provides an overview of drugs used for the treatment of depression and mania associated with bipolar disorder.

II. MECHANISM OF ANTIDEPRESSANT DRUGS

Most antidepressant drugs (Figure 17.1) either directly or indirectly potentiate the actions of norepinephrine and/or serotonin (5-HT) in the brain. This, along with other evidence, led to the biogenic amine theory, which proposes that depression is due to a deficiency of monoamines, such as norepinephrine and serotonin, at key sites in the brain. Conversely, the theory proposes that mania is caused by an overproduction of these neurotransmitters. However, the biogenic amine theory of depression and mania is overly simplistic. It fails to explain the time course for a therapeutic response with antidepressants, which usually occurs over several weeks or months, compared with the pharmacodynamic effects of the agents, which are usually immediate. This suggests that decreased reuptake of neurotransmitters is only an

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initial effect of the drugs, which may not be directly responsible for the antidepressant effects.

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SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

Citalopram CELEXA
Escitalopram LEXAPRO
Fluoxetine PROZAC
Fluvoxamine LUVOX
Paroxetine PAXIL
Sertraline ZOLOFT

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)

Desvenlafaxine PRISTIQ
Duloxetine CYMBALTA
Levomilnacipran FETZIMA
Venlafaxine EFFEXOR

ATYPICAL ANTIDEPRESSANTS

Brexanolone ZULRESSO
Bupropion WELLBUTRIN, ZYBAN
Esketamine SPRAVATO
Mirtazapine REMERON
Nefazodone GENERIC ONLY
Trazodone GENERIC ONLY
Vilazodone VIIBRYD
Vortioxetine TRINTELLIX

TRICYCLIC ANTIDEPRESSANTS (TCAs)

Amitriptyline GENERIC ONLY
Amoxapine GENERIC ONLY
Clomipramine ANAFRANIL
Desipramine NORPRAMIN
Doxepin SILENOR
Imipramine TOFRANIL
Maprotiline GENERIC ONLY
Nortriptyline PAMELOR
Protriptyline GENERIC ONLY
Trimipramine SURMONTIL

MONOAMINE OXIDASE INHIBITORS

Isocarboxazid MARPLAN
Phenelzine NARDIL

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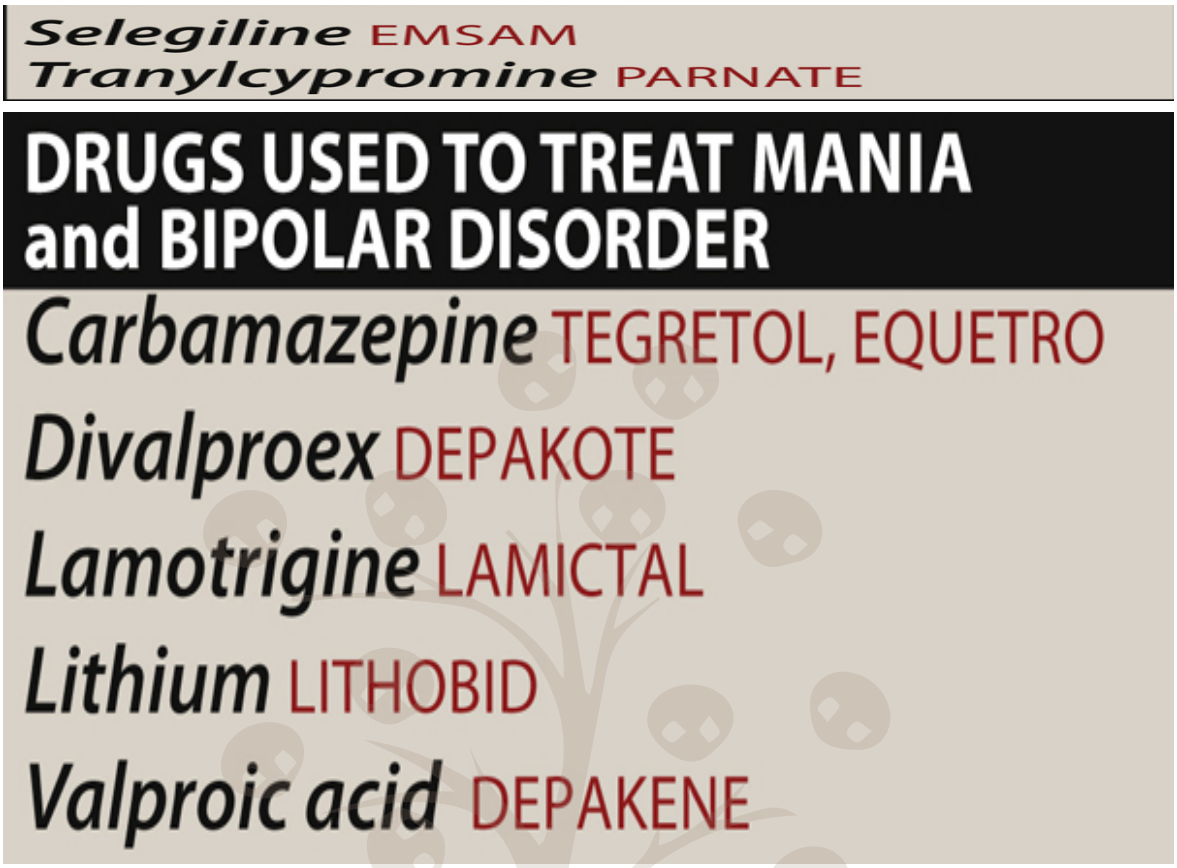

Figure 17.1 Summary of antidepressants.

III. SELECTIVE SEROTONIN REUPTAKE INHIBITORS

The selective serotonin reuptake inhibitors (SSRIs) are a group of antidepressant drugs that specifically inhibit serotonin reuptake, having much greater selectivity for the serotonin transporter, as compared with the norepinephrine transporter. This contrasts with the tricyclic antidepressants (TCAs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) that inhibit the reuptake of both norepinephrine and serotonin (Figure 17.2). Moreover, the SSRIs have little blocking activity at muscarinic, α-adrenergic, and histamine H_1 receptors. Because they have different adverse effects and are relatively safe in overdose, the SSRIs have replaced TCAs and monoamine oxidase inhibitors (MAOIs) as the drugs of choice in treating depression. The SSRIs include

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fluoxetine [floo-OX-e-teen] (the prototypic drug), *citalopram* [sye-TAL-oh-pram], *escitalopram* [es-sye-TAL-oh-pram], *fluvoxamine* [floo-VOX-e-meen], *paroxetine* [pa-ROX-e-teen], and *sertraline* [SER-tra-leen]. *Escitalopram* is the pure S-enantiomer of *citalopram*.

DRUG	UPTAKE INHIBITION	
	Norepinephrine	Serotonin
Selective serotonin reuptake inhibitor		
Fluoxetine	0	++++
Serotonin-norepinephrine reuptake inhibitors		
Venlafaxine*	++	++++
Duloxetine	++++	++++
Tricyclic antidepressants		
Imipramine	+++	++++
Nortriptyline	++++	++

Figure 17.2 Relative receptor specificity of some antidepressant drugs.**Venlafaxine* inhibits norepinephrine reuptake only at high doses. ++++ = very strong affinity; +++ = strong affinity; ++ = moderate affinity; + = weak affinity; 0 = little or no affinity.

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A. Actions

The SSRIs block the reuptake of serotonin, leading to increased concentrations of the neurotransmitter in the synaptic cleft. Antidepressants, including SSRIs, typically take at least 2 weeks to produce significant improvement in mood, and maximum benefit may require up to 12 weeks or more (Figure 17.3).

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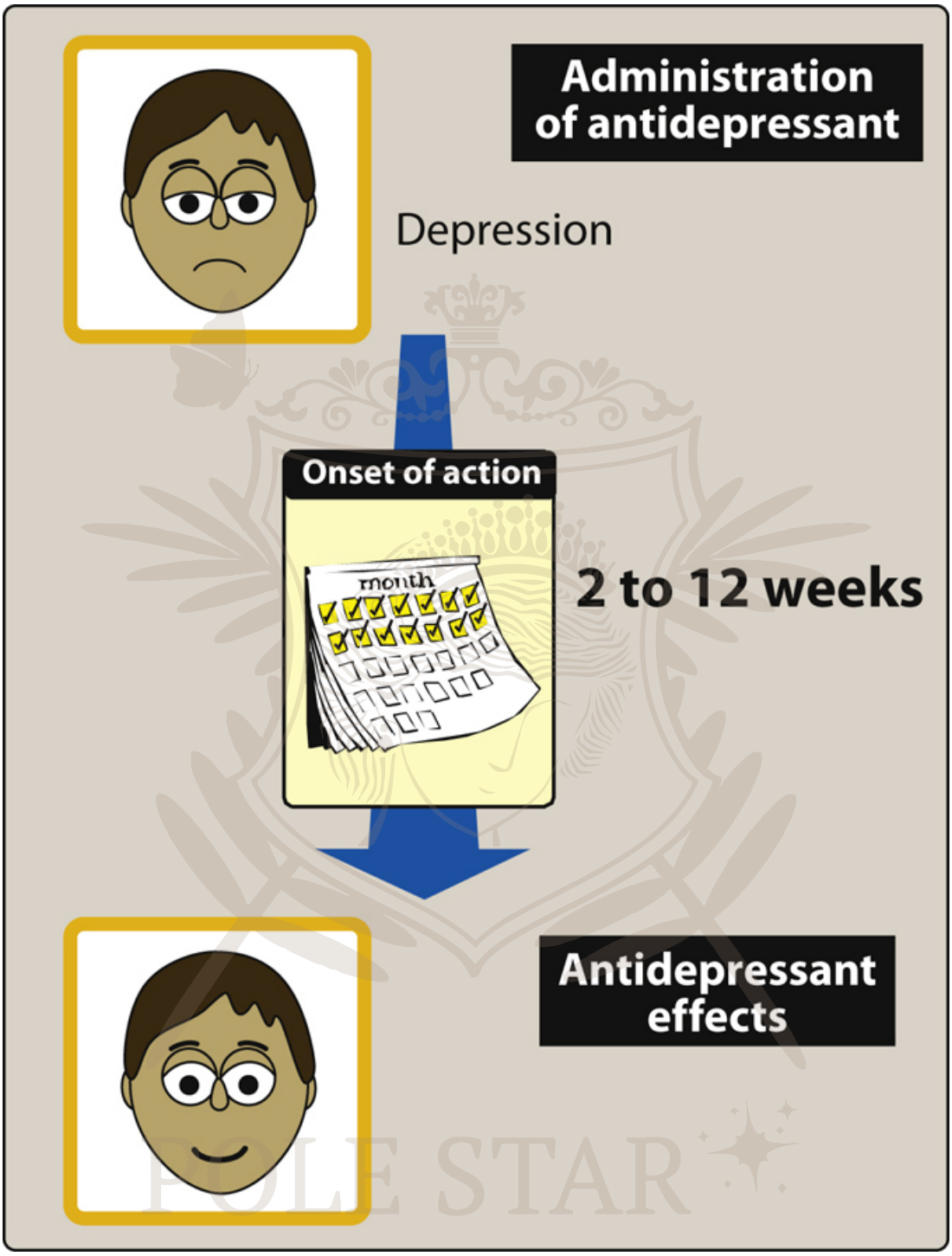

Figure 17.3 Onset of therapeutic effects of the major antidepressant drugs requires several weeks.

B. Therapeutic uses

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The primary indication for SSRIs is depression. A number of other psychiatric disorders also respond favorably to SSRIs, including obsessive–compulsive disorder, panic disorder, generalized anxiety disorder, posttraumatic stress disorder, social anxiety disorder, premenstrual dysphoric disorder, and bulimia nervosa (only *fluoxetine* is approved for bulimia).

C. Pharmacokinetics

All of the SSRIs are well absorbed after oral administration. Peak levels are seen in approximately 2 to 8 hours on average. Food has little effect on absorption (except with *sertraline*, for which food increases its absorption). The majority of SSRIs have plasma half-lives that range between 16 and 36 hours. Metabolism by cytochrome P450 (CYP450)–dependent enzymes and glucuronide or sulfate conjugation occur extensively. *Fluoxetine* differs from the other members of the class by having a much longer half-life (50 hours), and the half-life of its active metabolite *S*-norfluoxetine is quite long, averaging 10 days. *Fluoxetine* and *paroxetine* are potent inhibitors of CYP2D6. In addition, *fluoxetine* and *fluvoxamine* are potent inhibitors of CYP2C19, and *fluvoxamine* is also a potent inhibitor of CYP1A2 and moderate inhibitor of CYP3A4.

D. Adverse effects

Although the SSRIs are considered to have fewer and less severe adverse effects than the TCAs and MAOIs, they are not without adverse effects. For example, they may cause headache, sweating, anxiety and agitation, hyponatremia, gastrointestinal (GI) effects (nausea, vomiting, and diarrhea), weakness and fatigue, sexual dysfunction, changes in weight, sleep disturbances (insomnia and somnolence), and QT prolongation. In addition, these agents have the potential for drug–drug interactions (Figure 17.4). Some SSRIs are more likely to cause specific adverse effects. For example, *citalopram* is more likely to cause QT prolongation compared with other SSRIs. For this reason, patients who do not tolerate one SSRI may tolerate another SSRI.

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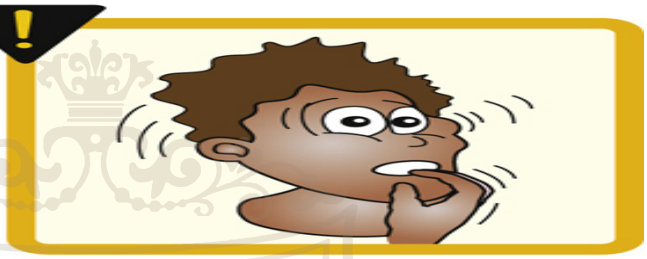
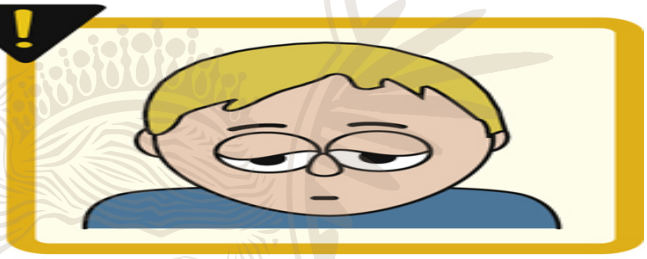
Nausea

Anxiety

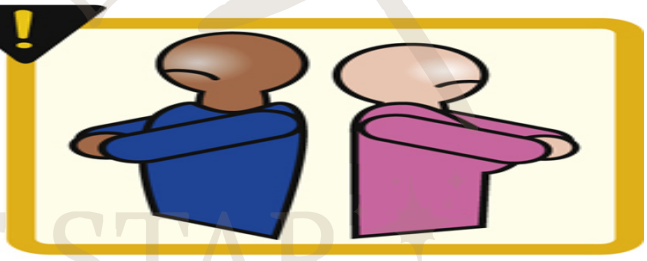


Drowsiness



Insomnia

Sexual dysfunction



Drug interactions

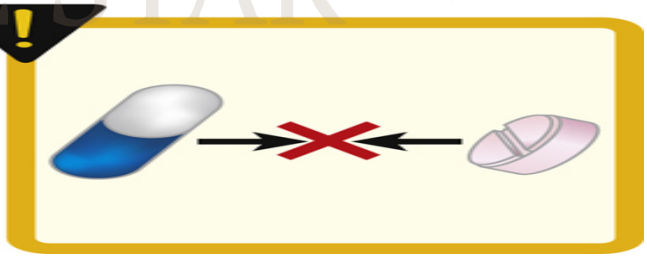


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Figure 17.4 Some commonly observed adverse effects of selective serotonin reuptake inhibitors.

1.Sleep disturbances: *Paroxetine* and *fluvoxamine* are generally more sedating than activating, and they may be useful in patients who have difficulty sleeping. Conversely, patients who are fatigued or complaining of excessive somnolence may benefit from one of the more activating SSRIs, such as *fluoxetine* or *sertraline*.

2.Sexual dysfunction: Sexual dysfunction, which may include loss of libido, delayed ejaculation, and anorgasmia, is common with the SSRIs. [Note: SSRIs are considered a first-line treatment strategy for the management of premature ejaculation.]

3.Use in children and adolescents: Antidepressants should be used cautiously in children and adolescents, because of increased risk of suicidal ideation with treatment. This precaution includes not only the SSRIs but other major categories of antidepressants (SNRIs, TCAs, MAOIs, and the atypical antidepressants) as well. Pediatric patients should be observed for worsening depression and suicidal thinking with initiation or dosage change of any antidepressant. *Fluoxetine*, *sertraline*, and *fluvoxamine* are approved for use in children to treat obsessive–compulsive disorder. *Fluoxetine* and *escitalopram*, along with some TCAs, are approved to treat childhood depression.

4.Overdose: An overdose with SSRIs does not usually cause cardiac arrhythmias, with the exception of *citalopram*, which may cause QT prolongation. Seizures are a possibility because all antidepressants may lower the seizure threshold. SSRIs have the potential to cause serotonin syndrome, especially when used in the presence of an MAOI or other highly serotonergic drug. Serotonin syndrome may include the symptoms of hyperthermia, muscle rigidity, sweating, myoclonus (clonic muscle twitching), and changes in mental status and vital signs.

5.Discontinuation syndrome: SSRIs have the potential to cause a discontinuation syndrome after their abrupt withdrawal, particularly the agents with shorter half-lives and inactive

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metabolites. *Fluoxetine* has the lowest risk of causing an SSRI discontinuation syndrome due to its longer half-life and active metabolite. Possible signs and symptoms of SSRI discontinuation syndrome include headache, malaise and flu-like symptoms, agitation and irritability, nervousness, and changes in sleep pattern. Gradual tapering of the SSRIs is recommended to prevent or reduce symptoms of discontinuation syndrome.

IV. SEROTONIN–NOREPINEPHRINE REUPTAKE INHIBITORS

Venlafaxine [VEN-la-fax-een], *desvenlafaxine* [dez-VEN-la-fax-een], *levomilnacipran* [lee-voe-mil-NA-si-pran], and *duloxetine* [doo-LOX-e-teen] inhibit the reuptake of both serotonin and norepinephrine (Figure 17.5) and, thus, are termed SNRIs. Depression is often accompanied by chronic pain, such as backache and muscle aches, for which SSRIs are relatively ineffective. This pain is, in part, modulated by serotonin and norepinephrine pathways in the central nervous system. With dual inhibition of serotonin and norepinephrine reuptake, both the SNRIs and the TCAs may be effective in relieving pain. These agents are also used in the treatment of pain syndromes, such as diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia, and low back pain. The SNRIs, unlike the TCAs, have little activity at α-adrenergic, muscarinic, or histamine receptors and, thus, have fewer receptor-mediated adverse effects than the TCAs. Some adverse effects are similar to those of SSRIs, including nausea and sexual dysfunction. Dizziness and diaphoresis can also occur. The SNRIs may also precipitate a discontinuation syndrome if treatment is abruptly stopped.

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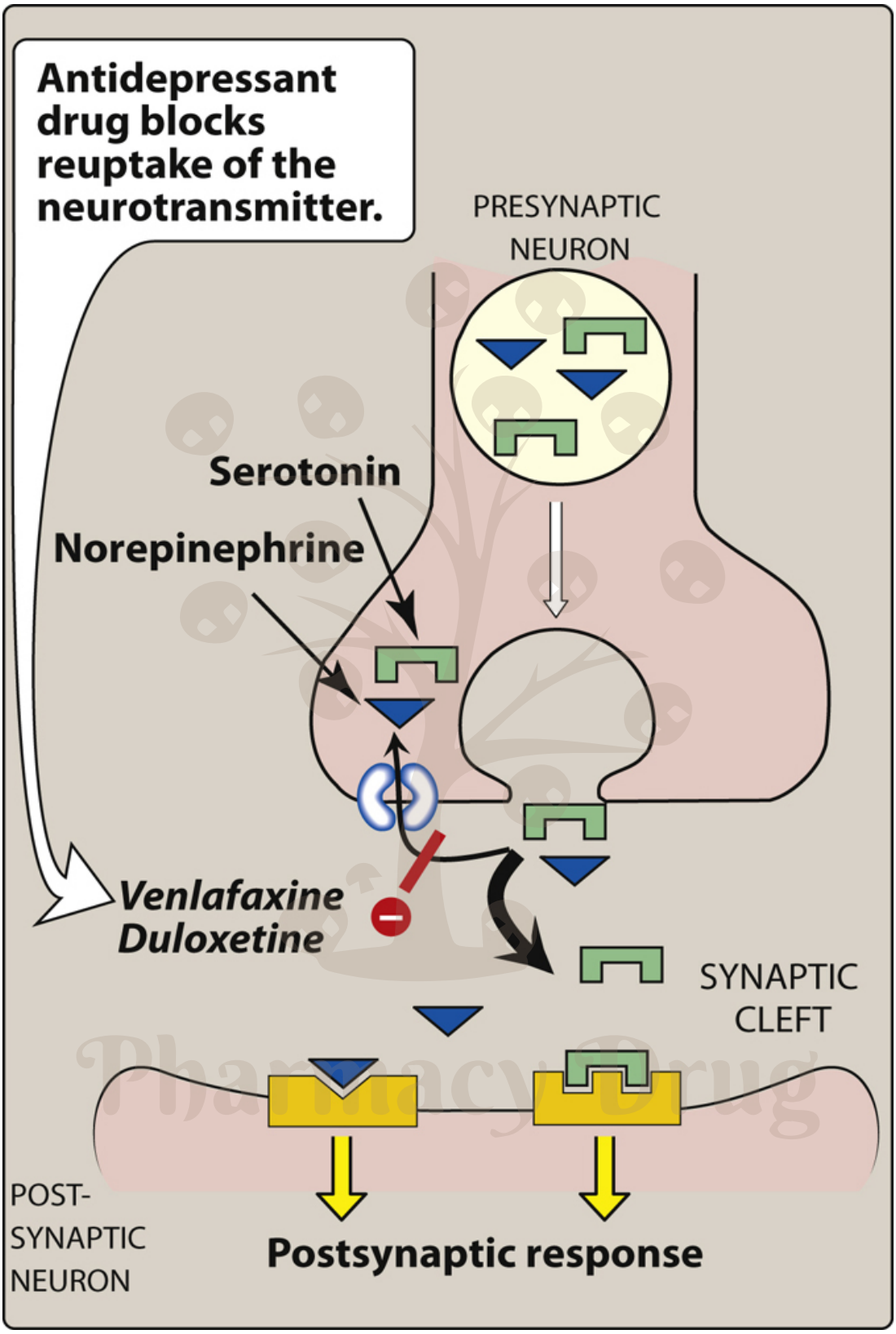

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Figure 17.5 Proposed mechanism of action of selective serotonin–norepinephrine reuptake inhibitor antidepressant drugs.

A. Venlafaxine and desvenlafaxine

Venlafaxine is an inhibitor of serotonin reuptake and, at medium to higher doses, is an inhibitor of norepinephrine reuptake. *Venlafaxine* has minimal inhibition of the CYP450 isoenzymes and is a substrate of the CYP2D6 isoenzyme. *Desvenlafaxine* is the active, demethylated metabolite of *venlafaxine.* The most common side effects of *venlafaxine* are nausea, headache, sexual dysfunction, dizziness, insomnia, sedation, and constipation. At high doses, there may be an increase in blood pressure and heart rate. The clinical activity and adverse effect profile of *desvenlafaxine* are similar to that of *venlafaxine*.

B. Duloxetine

Duloxetine inhibits serotonin and norepinephrine reuptake at all doses. It is extensively metabolized in the liver to inactive metabolites and should be avoided in patients with liver dysfunction. GI side effects are common with *duloxetine*, including nausea and constipation. Dry mouth, insomnia, dizziness, somnolence, sweating, and sexual dysfunction are also seen. *Duloxetine* may increase blood pressure or heart rate. It is a moderate inhibitor of CYP2D6 isoenzymes and may increase concentrations of drugs metabolized by this pathway, such as antipsychotics.

C. Levomilnacipran

Levomilnacipran is an enantiomer of *milnacipran* (an older SNRI used for the treatment of depression in Europe and fibromyalgia in the United States). The adverse effect profile of *levomilnacipran* is similar to that of other SNRIs, including nausea, headache, and dry mouth. It is primarily metabolized by CYP3A4, and, thus, activity may be altered by inducers or inhibitors of this enzyme system.

V. ATYPICAL ANTIDEPRESSANTS

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The atypical antidepressants are a mixed group of agents that have actions at several different sites. This group includes *brexanolone* [brex-AN-oh-lone], *bupropion* [byoo-PROE-pee-on], *esketamine* [es-KET-a-meen], *mirtazapine* [mir-TAZ-a-peen], *nefazodone* [ne-FAZ-oh-done], *trazodone* [TRAZ-oh-done], *vilazodone* [vil-AZ-oh-done], and *vortioxetine* [vor-TEE-ox-e-teen].

A. Brexanolone

Brexanolone is a positive allosteric modulator of $GABA_A$ receptors that is used for the treatment of postpartum depression. This agent is an analog of the neurosteroid allopregnanolone (a metabolite of progesterone). After delivery, levels of allopregnanolone decline, and this may be related to the etiology of postpartum depression. *Brexanolone* is administered as an intravenous infusion over 60 hours in an inpatient setting for women suffering from postpartum depression. A risk for excessive sedation, sudden loss of consciousness, and hypoxia are potential adverse events that warrant supervision and monitoring with use of this agent. The patient should be supervised when interacting with her child (or children) during treatment.

B. Bupropion

Bupropion is a weak dopamine and norepinephrine reuptake inhibitor that is used to alleviate the symptoms of depression. *Bupropion* is also useful for decreasing cravings and attenuating withdrawal symptoms of nicotine in patients trying to quit smoking (potentially though decreasing the stimulant effects of nicotine on the nicotinic acetylcholine receptors). Side effects may include dry mouth, sweating, nervousness, tremor, and a dose-dependent increased risk for seizures. It has a very low incidence of sexual dysfunction and may be used in patients who are concerned about the risk of antidepressant-related sexual dysfunction. *Bupropion* is metabolized by the CYP2B6 pathway and has a relatively low risk for drug–drug interactions, given the few agents that inhibit/induce this enzyme. The use of *bupropion* should be avoided in patients at risk for seizures, including those with concurrent electrolyte abnormalities or those with a history of anorexia or bulimia.

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C. Esketamine

Esketamine, the S-enantiomer of racemic *ketamine* (an anesthetic agent), is a nonselective, noncompetitive antagonist of the *N*-methyl-d-aspartate glutamate receptor. *Esketamine* is considered faster acting than standard antidepressants. The drug is administered intranasally as an adjunctive therapy for management of treatment-resistant depression or major depressive disorder with suicidal ideation or behavior. Due to the risks of sedation and feelings of dissociation that may occur with use of this agent, *esketamine* is administered in a controlled environment where patients must be monitored closely for 2 hours after administration. It is a controlled substance because of these risks, as well as its risks for abuse and misuse. Acute adverse events after treatment include sedation, nausea and vomiting, dissociation and hallucinations, and increased blood pressure.

D. Mirtazapine

Mirtazapine enhances serotonin and norepinephrine neurotransmission by serving as an antagonist at central presynaptic α_2 receptors. Additionally, some of the antidepressant activity may be related to antagonism at 5-HT_2 receptors. *Mirtazapine* is sedating because of its potent antihistaminic activity, but it does not cause the antimuscarinic side effects of the TCAs or interfere with sexual function like the SSRIs. Sedation, dry mouth, increased appetite, and weight gain frequently occur (Figure 17.6).

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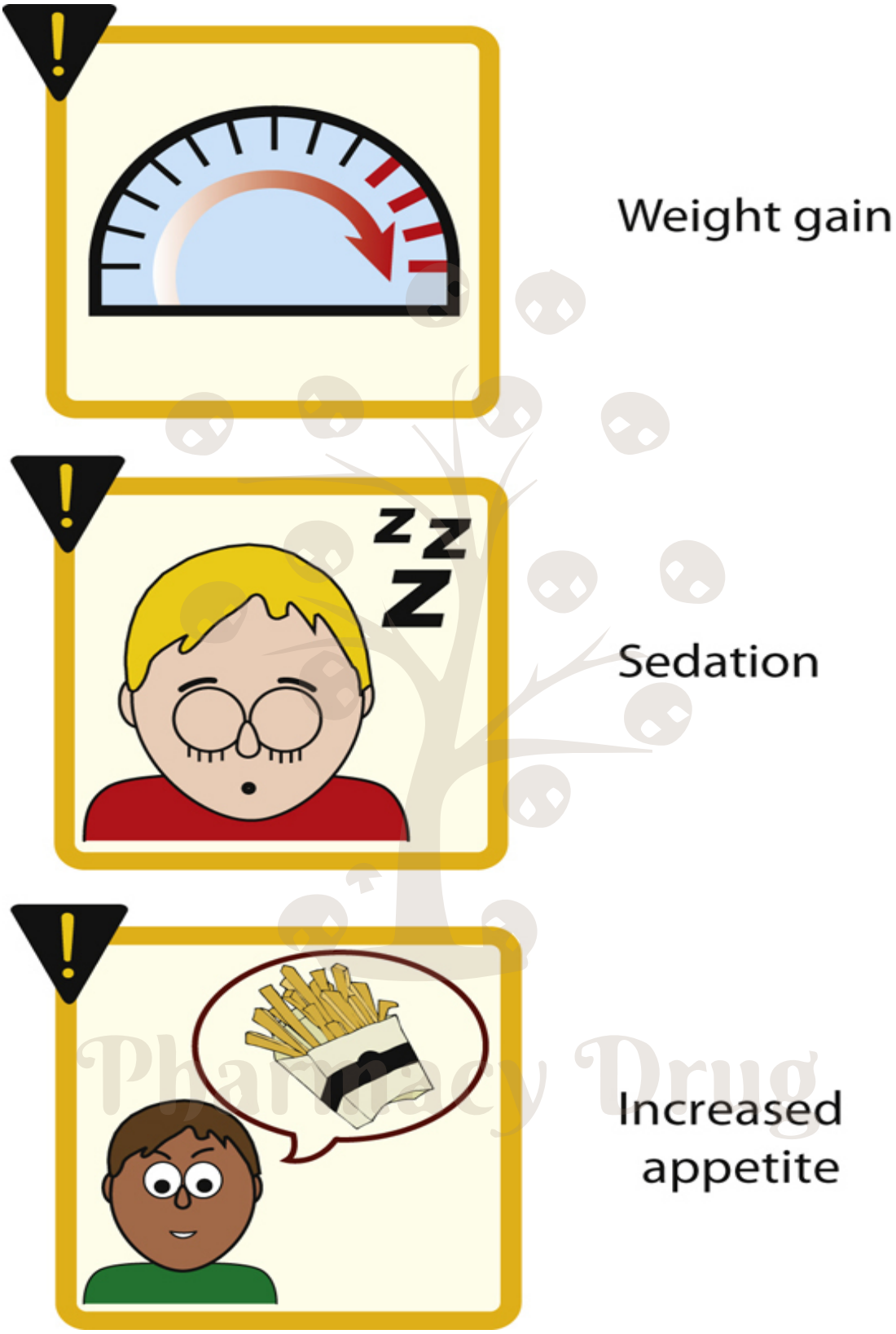

Figure 17.6 Some commonly observed adverse effects of *mirtazapine*.

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E. Nefazodone and trazodone

Nefazodone and *trazodone* are weak inhibitors of serotonin reuptake and norepinephrine reuptake and are also antagonists at the postsynaptic 5-HT_{2a} receptor. Both agents are sedating, probably because of their potent histamine H_1-blocking activity. *Trazodone* is commonly used off-label for the management of insomnia. Drug interactions must be considered, as these agents are both metabolized by CYP3A4. In addition, *nefazodone* is a potent inhibitor of CYP3A4. *Trazodone* has been associated with priapism, and *nefazodone* has been associated with a risk for hepatotoxicity. Both agents also have mild-to-moderate α_1 receptor antagonism, contributing to orthostasis and dizziness. Nausea and dry mouth are also potential side effects of these agents.

F. Vilazodone

Vilazodone is a serotonin reuptake inhibitor and a 5-HT_{1a} receptor partial agonist. Although the extent to which the 5-HT_{1a} receptor activity contributes to its therapeutic effects is unknown, this possible mechanism of action renders it unique from that of the SSRIs. *Vilazodone* is metabolized by CYP3A4, and strong inhibitors or inducers of CYP3A4 may significantly increase or decrease levels, respectively. The adverse effect profile is similar to that of the SSRIs and includes nausea, diarrhea, sexual dysfunction, and dizziness. In addition, *vilazodone* has a risk for discontinuation syndrome if abruptly stopped.

G. Vortioxetine

Vortioxetine utilizes a combination of serotonin reuptake inhibition, 5-HT_{1a} agonism, and 5-HT_3 and 5-HT_7 antagonism as its proposed mechanisms of action to treat depression. It is unclear to what extent the activities other than inhibition of serotonin reuptake influence the overall effects of *vortioxetine.* This agent is primarily metabolized by CYP2D6, and a dosage reduction is recommended when *vortioxetine* is coadministered with strong CYP2D6 inhibitors. The common

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adverse effects include nausea, constipation, and sexual dysfunction, which may be expected due to its serotonergic mechanisms.

VI. TRICYCLIC ANTIDEPRESSANTS

Similar to the SNRIs, the TCAs inhibit norepinephrine and serotonin reuptake into the presynaptic neuron. The primary difference between these two drug classes is the more benign side effect profile of SNRIs, as TCAs also affect several other receptor types. The TCAs include the tertiary amines *imipramine* [ee-MIP-ra-meen] (the prototype drug), *amitriptyline* [a-mee-TRIP-ti-leen], *clomipramine* [kloe-MIP-ra-meen], *doxepin* [DOX-e-pin], and *trimipramine* [trye-MIP-ra-meen] and the secondary amines *desipramine* [dess-IP-ra-meen] and *nortriptyline* [nor-TRIP-ti-leen] (the *N*-demethylated metabolites of *imipramine* and *amitriptyline*, respectively) and *protriptyline* [proe-TRIP-ti-leen]. *Maprotiline* [ma-PROE-ti-leen] and *amoxapine* [a-MOX-a-peen] are related "tetracyclic" antidepressant agents and are commonly included in the general class of TCAs.

A. Mechanism of action

1.Inhibition of neurotransmitter reuptake: TCAs and *amoxapine* are potent inhibitors of the neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals. *Maprotiline* and *desipramine* are relatively selective inhibitors of norepinephrine reuptake.

2.Blocking of receptors: TCAs also block serotonergic, α-adrenergic, muscarinic, and histamine H_1 receptors. It is not known if any of these actions produce the therapeutic benefit of the TCAs. However, actions at these receptors are likely responsible for many of their adverse effects. *Amoxapine* also blocks 5-HT_2 and dopamine D_2 receptors.

B. Actions

The TCAs improve mood in 50% to 70% of individuals with major depression. Like most antidepressants, the onset of the mood elevation is slow, requiring 2 weeks or longer (Figure 17.3). Patient

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response can be used to adjust dosage. Tapering of these agents is recommended to minimize discontinuation syndromes and cholinergic rebound effects.

C. Therapeutic uses

The TCAs are effective in treating moderate to severe depression. Some patients with panic disorder also respond to TCAs. *Imipramine* is used as an alternative to *desmopressin* or nonpharmacologic therapies (enuresis alarms) in the treatment of bed-wetting in children. The TCAs, particularly *amitriptyline*, have been used to help prevent migraine headache and treat chronic pain syndromes (for example, neuropathic pain) in a number of conditions for which the cause of pain is unclear. Low doses of TCAs, especially *doxepin*, can be used to treat insomnia.

D. Pharmacokinetics

TCAs are well absorbed upon oral administration. As a result of their variable first-pass metabolism in the liver, TCAs have low and inconsistent bioavailability. These drugs are metabolized by the hepatic microsomal system (and, thus, may be sensitive to agents that induce or inhibit the CYP450 isoenzymes) and conjugated with glucuronic acid. Ultimately, the TCAs are excreted as inactive metabolites via the kidney.

E. Adverse effects

Blockade of muscarinic receptors leads to blurred vision, xerostomia, urinary retention, sinus tachycardia, constipation, and aggravation of angle-closure glaucoma (Figure 17.7). These agents affect cardiac conduction similar to *quinidine* and may precipitate life-threatening arrhythmias in an overdose situation. The TCAs also block α-adrenergic receptors, causing orthostatic hypotension, dizziness, and reflex tachycardia. Sedation is related to the ability of these drugs to block histamine H_1 receptors. Weight gain is a common adverse effect of the TCAs. Sexual dysfunction occurs in a minority of patients, and the incidence is lower than that associated with the SSRIs.

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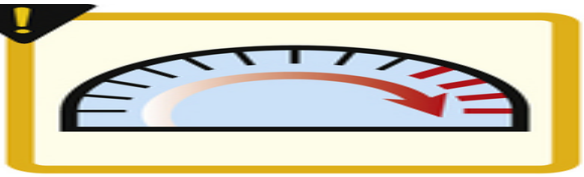
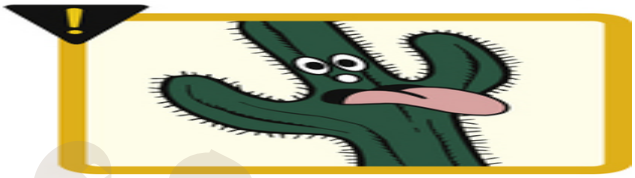
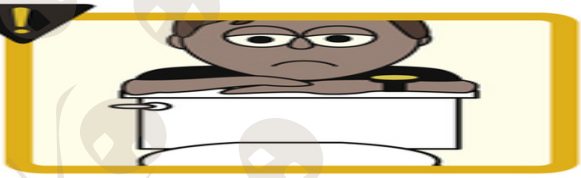
Weight gain



Dry mouth



Constipation

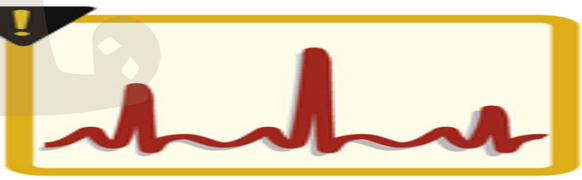


Urinary retention

Blurred vision

Tachycardia

Arrhythmias



Nausea

Drowsiness

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Figure 17.7 Some commonly observed adverse effects of tricyclic antidepressants.

All antidepressants, including TCAs, should be used with caution in patients with bipolar disorder, even during their depressed state, because antidepressants may cause a switch to manic behavior. The TCAs have a narrow therapeutic index (for example, five- to six-fold the maximal daily dose of *imipramine* can be lethal). Depressed patients who are suicidal should be given only limited quantities of these drugs and be monitored closely. Drug interactions with the TCAs are shown in Figure 17.8. The TCAs may exacerbate certain medical conditions, such as benign prostatic hyperplasia, epilepsy, and preexisting arrhythmias.

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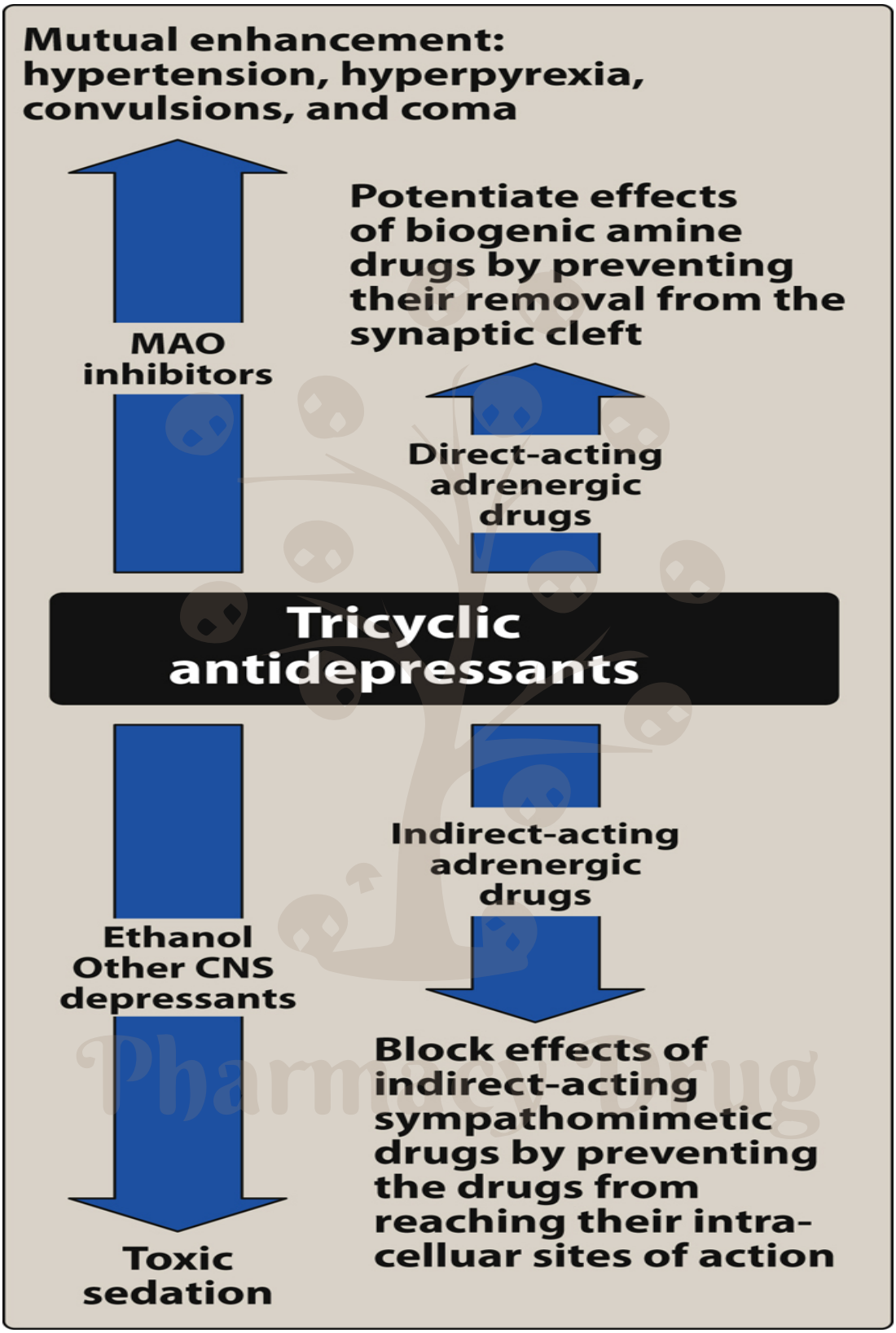

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Figure 17.8 Drugs interacting with tricyclic antidepressants.CNS = central nervous system; MAO = monoamine oxidase.

VII. MONOAMINE OXIDASE INHIBITORS

Monoamine oxidase (MAO) is a mitochondrial enzyme found in nerve and other tissues, such as the gut and liver. In the neuron, MAO functions as a "safety valve" to oxidatively deaminate and inactivate any excess neurotransmitters (for example, norepinephrine, dopamine, and serotonin) that may leak out of synaptic vesicles when the neuron is at rest. Of the two isozymes of MAO, MAO-A metabolizes serotonin, norepinephrine, and dopamine and MAO-B primarily metabolizes dopamine. The MAOIs may irreversibly or reversibly inactivate the enzyme, permitting neurotransmitters to escape degradation and, therefore, to accumulate within the presynaptic neuron and leak into the synaptic space. The four MAOIs currently available for the treatment of depression include *phenelzine* [FEN-el-zeen], *tranylcypromine* [tran-il-SIP-roe-meen], *isocarboxazid* [eye-soe-car-BOX-ih-zid], and *selegiline* [seh-LEDGE-ah-leen]. All are nonselective for inhibition of MAO-A and MAO-B, except for *selegiline*, which is more selective for MAO-B at lower doses but considered nonselective at high doses. [Note: *Selegiline* is also used for the treatment of Parkinson disease. It is the only antidepressant available in a transdermal delivery system.] The use of MAOIs is limited due to the potential severity of drug–drug and drug–food interactions while taking these agents.

A. Mechanism of action

Most MAOIs, such as *phenelzine*, form stable complexes with the enzyme, causing irreversible inactivation. This results in increased stores of norepinephrine, serotonin, and dopamine within the neuron and subsequent diffusion of excess neurotransmitter into the synaptic space (Figure 17.9). These drugs inhibit not only MAO in the brain but also MAO in the liver and gut that catalyzes oxidative deamination of drugs and potentially toxic substances, such as tyramine, which is found in certain foods. The MAOIs, therefore, show a high incidence of drug–drug and drug–food interactions. *Selegiline* administered as

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the transdermal patch may produce less inhibition of gut and hepatic MAO at low doses because it avoids first-pass metabolism.

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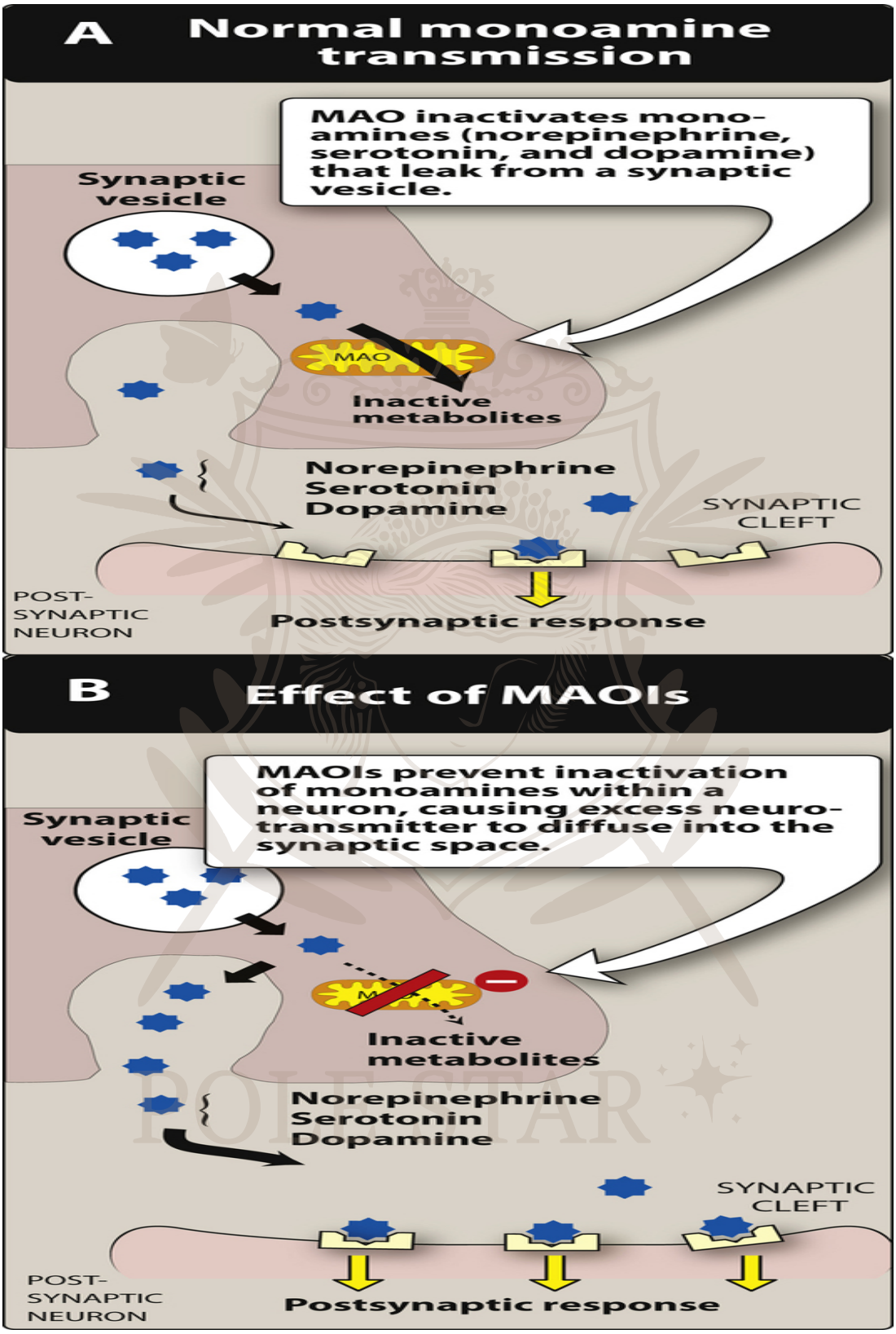

Figure 17.9 Mechanism of action of monoamine oxidase inhibitors (MAOIs).

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B. Actions

Although MAO is fully inhibited after several days of treatment, the antidepressant action of the MAOIs, like that of the SSRIs, SNRIs, and TCAs, is delayed several weeks. *Selegiline* and *tranylcypromine* have an amphetamine-like stimulant effect that may produce agitation or insomnia.

C. Therapeutic uses

The MAOIs are indicated for depressed patients who are unresponsive or intolerant of other antidepressants. Because of their risk for drug–drug and drug–food interactions, the MAOIs are considered last-line agents in many treatment settings.

D. Pharmacokinetics

These drugs are well absorbed after oral administration. Time to regeneration of the MAO enzyme following irreversible inactivation by MAOIs varies, but it usually occurs several weeks after termination of the drug. Thus, when switching antidepressant agents, a minimum of 2 weeks of delay must be allowed after termination of MAOI therapy and the initiation of another antidepressant from any other class. MAOIs are hepatically metabolized and excreted rapidly in urine.

E. Adverse effects

Severe and often unpredictable side effects, due to drug–food and drug–drug interactions, limit the widespread use of MAOIs. For example, tyramine, which is contained in aged cheeses and meats, liver, pickled or smoked fish, and red wine, is normally inactivated by MAO-A in the gut. Individuals receiving a nonselective MAOI are unable to degrade tyramine obtained from the diet. Tyramine causes the release of large amounts of stored catecholamines from nerve terminals, resulting in a hypertensive crisis, with signs and symptoms such as occipital headache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures, and, possibly, stroke. Patients must be educated to avoid tyramine-containing foods. Other possible adverse effects of treatment with MAOIs include drowsiness, orthostatic hypotension, blurred vision, dry mouth, and constipation.

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SSRIs should not be coadministered with MAOIs due to the risk of serotonin syndrome. Both SSRIs and MAOIs require a washout period of at least 2 weeks before the other type is administered, with the exception of *fluoxetine*, which should be discontinued at least 6 weeks before an MAOI is initiated. In addition, the MAOIs have many other critical drug interactions, and caution is required when administering these agents concurrently with other drugs. For example, when MAOIs are combined with direct or indirect sympathomimetics, such as *pseudoephedrine*, it can lead to significant hypertension. Figure 17.10 summarizes the side effects of the antidepressant drugs.

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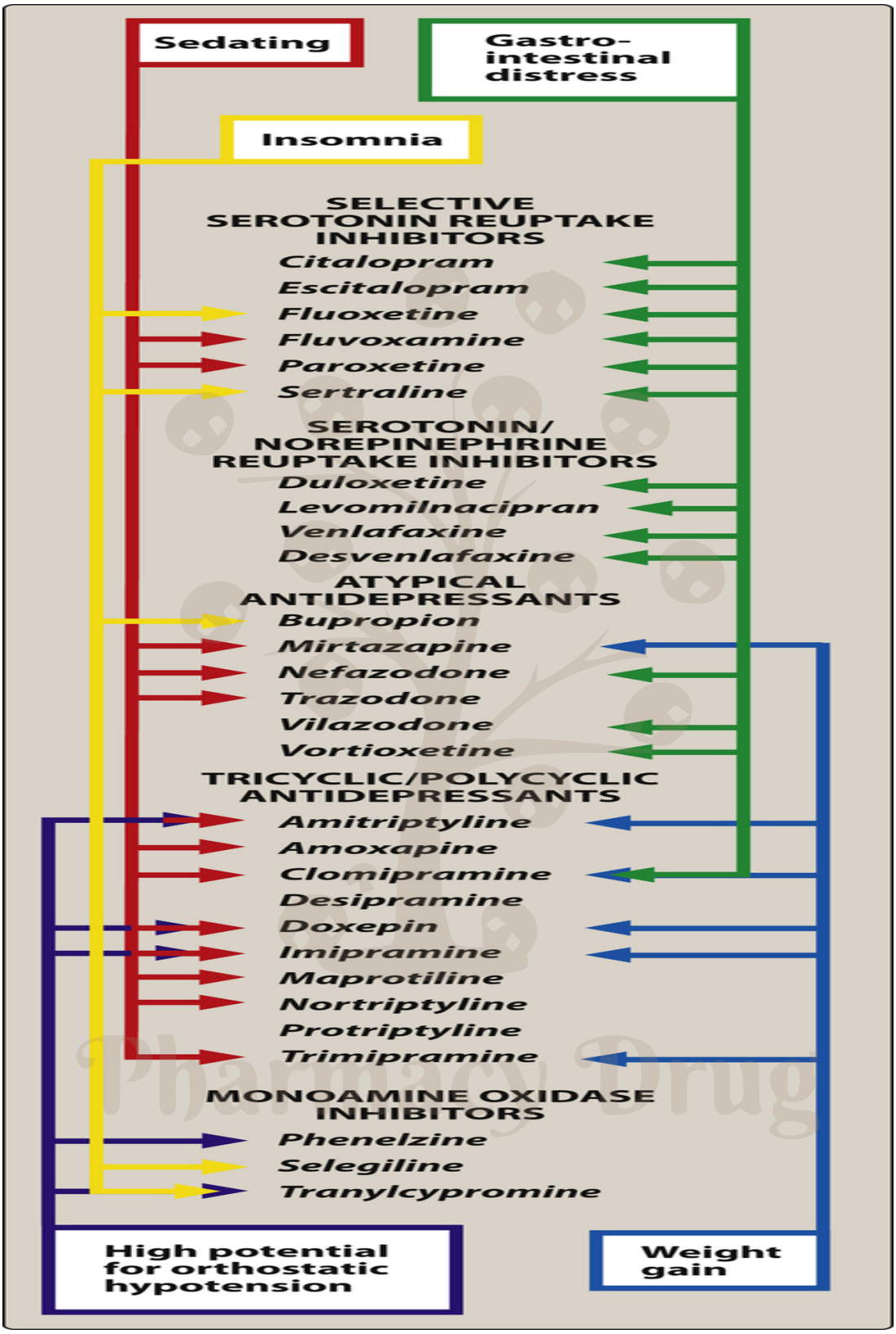

Figure 17.10 Side effects of some drugs used to treat depression.

A L G r a w a n y

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Clinical Application 17.1: Patient-specific Considerations in Antidepressant Drug Selection

Given that many antidepressants are considered equally efficacious despite having different mechanisms of action and side effect profiles, it becomes clinically meaningful to try to select the best antidepressant for a specific patient in an individualized and thoughtful process. Clinicians should consider the following primary aspects of the patient and the possible antidepressants when choosing a treatment: patient history of response to specific antidepressants, family history of response to antidepressants, concurrent medical and psychiatric conditions, adverse effect profile of the antidepressant being considered, and clinical presentation of the depressive symptoms. Secondary considerations may include age, medication cost, dosing regimen/frequency, drug–drug or drug–food interactions, genetic factors, stigma surrounding some medications, nonpharmacological interventions, and history of adherence with prior treatments.

VIII. SEROTONIN–DOPAMINE ANTAGONISTS

While 60% to 80% of patients respond favorably to antidepressants, 20% to 40% experience a partial or poor response to monotherapy. The second-generation antipsychotics (SGAs), also referred to as atypical antipsychotics, block serotonin (5-HT_2) and dopamine (D_2) receptors (see Chapter 18). SGAs are used as adjunctive treatments in patients without a complete response to antidepressant therapy. *Aripiprazole*, *brexpiprazole*, and *quetiapine* are approved for use as adjuncts in major depressive disorder (MDD), and the combination of *fluoxetine* and *olanzapine* is approved for treatment-resistant depression.

XI. TREATMENT OF MANIA AND BIPOLAR DISORDER

Improvements in the treatment of bipolar disorder have occurred because of increased recognition of this mood disorder, as well as an

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increase in the number of available medications for the treatment of mania.

A. Lithium

Lithium salts are used acutely and prophylactically for management of bipolar disorder. *Lithium* is effective in treating 60% to 80% of patients exhibiting mania and hypomania. Although many cellular processes are altered by treatment with *lithium*, the mode of action is not fully understood. *Lithium* is a monovalent cation that is thought to have various mechanisms, including effects on second messenger and intracellular signal transduction. It may also have neuroprotective effects. The therapeutic index of *lithium* is extremely low, and serum concentrations of *lithium* should be monitored during treatment. Common adverse effects may include headache, dry mouth, polydipsia, polyuria, polyphagia, GI distress, fine hand tremor, dizziness, fatigue, dermatologic reactions, and sedation. Adverse effects such as ataxia, slurred speech, coarse tremors, confusion, and convulsions indicate higher plasma levels and potential *lithium* toxicity. Use of *lithium* has been associated with development of nephrogenic diabetes insipidus, particularly with long-term treatment. Thyroid function may be decreased and should be monitored. *Lithium* is renally eliminated, and caution should be used when dosing this drug in renally impaired patients. *Lithium* may be the best choice for mood stabilization in patients with hepatic impairment.

B. Other drugs

Several antiepileptic drugs, including *carbamazepine*, *divalproex* (a prodrug which becomes *valproic acid* and *valproate* after ingestion), and *lamotrigine* (see Chapter 19), are approved as mood stabilizers for bipolar disorder. Other agents that may reduce manic symptoms include the older (*chlorpromazine* and *haloperidol*) antipsychotics and newer atypical second-generation antipsychotics. The atypical antipsychotics *risperidone*, *olanzapine*, *ziprasidone*, *aripiprazole*, *asenapine*, *cariprazine*, and *quetiapine* (see Chapter 18) are also used for the management of mania. *Quetiapine*, *lurasidone*, *cariprazine* and the combination of *olanzapine* and *fluoxetine* have been approved for bipolar depression.

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Chapter Summary

- The antidepressants, in general, have the pharmacodynamic goal of increasing or modulating the neurotransmitters of norepinephrine, serotonin, and dopamine. This is usually achieved with inhibition of reuptake transporters, receptor antagonism, or inhibition of monoamine oxidase.
- Newer, atypical antidepressants may act on other neurotransmitter systems such as GABA (*brexanolone*) or glutamate (*esketamine*).
- The SSRIs and newer SNRIs are more commonly prescribed, as they have multiple indications, are generally easier to use in patients with concurrent medical conditions, and are considered safer in overdose.
- Most antidepressants are considered equally efficacious, and thus selection of one agent over the other may be related to adverse-effect profiles and patient history of response. Newer agents are used for more specific aspects of depression such as treatment-resistant depression (*esketamine* or the combination of *olanzapine* and *fluoxetine*) or postpartum depression (*brexanolone*).
- The MAOIs are generally considered last-line treatment for depression, as they have multiple drug–food and drug–drug interactions that can be significant.
- Some second-generation antipsychotics are used as adjunctive treatments to antidepressants for refractory depression, such as *aripiprazole*, *brexpiprazole*, or *quetiapine.*
- Mood stabilizers, such as *lithium*, *divalproex sodium*, *carbamazepine*, and *lamotrigine* are the drugs of choice for maintenance of bipolar disorder, and some SGAs are effective for acute episodes of both manic symptoms and/or depressive symptoms.

STUDY QUESTIONS

Choose the ONE best answer.

17.1 A 55-year-old man is diagnosed with depression and started on treatment with fluoxetine. After 6 weeks of therapy his symptoms have improved, but he complains of sexual dysfunction. Which of the following drugs might be useful for the management of depression in this patient to minimize this adverse effect?

A. Sertraline
B. Citalopram
C. Mirtazapine
D. Lithium

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Correct answer = C. Mirtazapine is considered to have a low risk for sexual side effects. Sexual dysfunction commonly occurs with SSRIs (sertraline and citalopram), as well as with TCAs and SNRIs. Lithium is commonly used for the treatment of mania and bipolar disorder and is not indicated for this patient's depression.

17.2 A 36-year-old man presents with symptoms of compulsive behavior. He realizes that his behavior is interfering with his ability to accomplish his daily tasks but cannot seem to stop himself. Which of the following drugs would be most helpful to this patient?

A. Desipramine
B. Paroxetine
C. Amitriptyline
D. Selegiline

Correct answer = B. SSRIs are particularly effective in treating obsessive–compulsive disorder, and paroxetine is approved for this condition as well as being approved for depression. The other drugs are less effective in the treatment of obsessive–compulsive disorder. Patients with obsessive–compulsive disorder often have a concurrent depressive disorder.

17.3 Which of the following antidepressants causes 5-HT_{1a} receptor partial agonism and 5-HT reuptake inhibition?

A. Sertraline
B. Brexpiprazole
C. Maprotiline
D. Vilazodone

Correct answer = D. In addition to inhibition of serotonin reuptake, the antidepressant activity of vilazodone may be related to its 5-HT_{1a} receptor agonism. Although brexpiprazole is also proposed to have 5-HT_{1a} partial agonism, it is not considered to be a serotonin reuptake inhibitor. Sertraline is an SSRI with no appreciable 5-HT_{1a} partial agonism. Maprotiline is relatively selective for norepinephrine reuptake inhibition and also has no appreciable 5-HT_{1a} partial agonism.

17.4 A 45-year-old man complains of depression and difficulty sleeping. The physician would prefer to prescribe a drug that helps

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manage both the depression and insomnia. Which of the following antidepressants is the most appropriate to treat both indications?

A. Bupropion
B. Duloxetine
C. Doxepin
D. Levomilnacipran

Correct answer = C. Doxepin is the most sedating of the list due to its histamine-blocking activity. Doxepin is also used for the management of insomnia at low doses.

17.5 A 32-year-old patient is diagnosed with bipolar disorder. His past medical history is significant for hepatic impairment. Therefore, the prescriber prefers to use a medication that is renally eliminated. Which mood stabilizer may be most safe and effective for this patient?

A. Valproic acid
B. Carbamazepine
C. Lithium
D. Lamotrigine

Correct answer = C. Lithium is the only agent for bipolar disorder that does not require hepatic metabolism and, thus, may be dosed without issue in a hepatically impaired patient. However, if the patient had renal impairment, the lithium dosage would have to be adjusted.

17.6 A 75-year-old woman presents with complaints of lightheadedness and dizziness when standing up from a seated position. She reports these symptoms started after she began a new antidepressant a few weeks ago. She is diagnosed with orthostatic hypotension. Which of the following antidepressant agents has significant α_1 receptor antagonism and most likely caused these symptoms?

A. Venlafaxine
B. Bupropion
C. Escitalopram
D. Imipramine

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Correct answer = D. Venlafaxine, bupropion, and escitalopram have very little effect on decreasing blood pressure (no α_1 receptor antagonism) and are considered acceptable choices for treatment of depression in the elderly. Venlafaxine is more often associated with increased blood pressure (not hypotension). Imipramine is associated with a high risk for orthostasis in the elderly and should be avoided due to its adverse effect profile and risk for falls.

17.7 A 15-year-old patient was recently diagnosed with major depression and is not responding to psychotherapy. She has a history of two suicide attempts with over-the-counter drugs. Which of the following agents would be an appropriate first choice for this patient when used with close monitoring?

A. Escitalopram
B. Quetiapine
C. Vilazodone
D. Imipramine

Correct answer = A. The SSRI escitalopram is approved for use in adolescents. The TCAs, such as imipramine, are more dangerous in overdose compared with the SSRIs. Vilazodone is not approved for adolescents with major depression, and quetiapine is approved for adult patients (not adolescents) who have partially responded to adequate trials of antidepressant monotherapy.

17.8 A 45-year-old man is referred to a psychiatrist for the management of treatment-resistant depression after multiple failures of monotherapy with various antidepressants. Which of the following agents may be beneficial for use as an adjunctive therapy for management of treatment-resistant depression in this patient?

A. Amoxapine
B. Brexanolone
C. Risperidone
D. Esketamine

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Correct answer = D. Of the drugs listed, only esketamine is approved for adjunctive use with antidepressants for treatment-resistant depression. It is administered intranasally and only under the supervision of a healthcare professional due to multiple risks with its use.

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17.9 A 35-year-old woman with depression has had a partial response to sertraline but has been unable to achieve full remission of her depressive symptoms. Which of the following treatments is indicated as an adjunctive agent to assist in further improvement of her symptoms?

A. Maprotiline
B. Tranylcypromine
C. Aripiprazole
D. Brexanolone

Correct answer = C. Of the agents listed, only aripiprazole is approved as an adjunctive treatment for patients who have had a partial response to their monotherapy antidepressant. Quetiapine and brexpiprazole are also indicated for this type of partial response to antidepressants.

17.10 A 50-year-old man is diagnosed with major depression and generalized anxiety. His past medical history includes diabetes and diabetic neuropathy. Which of the following medications has the best chance of improving depression, anxiety, and neuropathic pain as a single treatment in this patient?

A. Fluoxetine
B. Citalopram
C. Vortioxetine
D. Duloxetine

Correct answer = D. Duloxetine is indicated for each condition (depression, generalized anxiety, and diabetic neuropathic pain). The other agents may improve depression and anxiety but are not considered as effective as duloxetine in managing chronic pain syndromes.

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18

Antipsychotic Drugs

Jose A. Rey

I. OVERVIEW

The antipsychotic drugs are used primarily to treat schizophrenia, but they are also effective in other psychotic and manic states. The use of antipsychotic medications involves a difficult trade-off between the benefit of alleviating symptoms related to psychosis and the risk of a wide variety of adverse effects. Antipsychotic drugs (Figure 18.1) are not curative and do not eliminate chronic thought disorders, but they often decrease the intensity of hallucinations and delusions and permit the patient with schizophrenia to function in a supportive environment.

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FIRST-GENERATION ANTIPSYCHOTIC (low potency)

Chlorpromazine GENERIC ONLY
Thioridazine GENERIC ONLY

FIRST-GENERATION ANTIPSYCHOTIC (high potency)

Fluphenazine GENERIC ONLY
Haloperidol HALDOL
Loxapine GENERIC ONLY
Molindone GENERIC ONLY
Perphenazine GENERIC ONLY
Pimozide ORAP
Prochlorperazine COMPRO, PROCOMP
Thiothixene GENERIC ONLY
Trifluoperazine GENERIC ONLY

SECOND-GENERATION ANTIPSYCHOTIC

Aripiprazole ABILIFY, ARISTADA
Asenapine SAPHRIS, SECUADO
Brexpiprazole REXULTI
Cariprazine VRAYLAR
Clozapine CLOZARIL
Iloperidone FANAPT
Lumateperone CAPLYTA
Lurasidone LATUDA
Olanzapine ZYPREXA
Paliperidone INVEGA
Pimavanserin NUPLAZID
Quetiapine SEROQUEL
Risperidone PERSERIS, RISPERDAL
Ziprasidone GEODON

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Figure 18.1 Summary of antipsychotic agents.

II. SCHIZOPHRENIA

Schizophrenia is a type of chronic psychosis characterized by positive symptoms such as delusions, hallucinations (often in the form of voices), disturbances in thought and behavior, and negative symptoms such as avolition or ambivalence. The onset of illness is often during late adolescence or early adulthood. It occurs in about 1% of the population and is a chronic and disabling disorder. Schizophrenia has a strong genetic component and probably reflects some fundamental developmental and biochemical abnormality, possibly a dysfunction of the mesolimbic or mesocortical dopaminergic neuronal pathways. There are four primary dopaminergic tracts of interest in managing schizophrenia with antipsychotics. The positive symptoms of the disorder are believed to be related to a hyperdopaminergic dysfunction of the mesolimbic tract. The negative symptoms and some cognitive dysfunction of the disorder may be related to a hypodopaminergic dysfunction in the mesocortical tract. Issues related to movement disorders are due to dopamine blockade in the nigrostriatal tract, and issues related to prolactin changes are due to dopamine blockade in the tuberoinfundibular tract.

III. ANTIPSYCHOTIC DRUGS

The antipsychotic drugs are usually divided into first- and second-generation agents. The first-generation drugs are further classified as “low potency” or “high potency.” This classification does not indicate clinical effectiveness of the drugs but rather specifies affinity for the dopamine D_2 receptor, which, in turn, may influence the adverse effect profile of the drug.

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A. First-generation antipsychotics

The first-generation antipsychotic drugs (FGAs, also historically called conventional antipsychotics, neuroleptics, and major tranquilizers) are competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competitive blockade of dopamine D_2 receptors. First-generation antipsychotics are more likely to be associated with movement disorders known as extrapyramidal symptoms (EPS), particularly drugs that bind tightly to dopaminergic neuroreceptors, such as *haloperidol* [HAL-oh-PER-i-dol]. Movement disorders are somewhat less likely with medications that bind less potently, such as *chlorpromazine* [klor-PROE-ma-zeen]. No one drug is clinically more effective than another.

B. Second-generation antipsychotics

The second-generation antipsychotic drugs (SGAs, also called "atypical" antipsychotics) have a lower incidence of EPS than the first-generation agents but are associated with a higher risk of metabolic adverse effects, such as diabetes, hypercholesterolemia, and weight gain. The second-generation drugs owe their unique activity to blockade of both serotonin 5-HT_2 and dopamine D_2 receptors.

1. **Drug selection:** Second-generation agents are generally used as first-line therapy for schizophrenia to minimize the risk of debilitating EPS associated with the first-generation drugs that act primarily at the dopamine D_2 receptor. The second-generation antipsychotics exhibit an efficacy that is equivalent to, and occasionally exceeds, that of the first-generation antipsychotic agents. Differences in therapeutic efficacy among the second-generation drugs have not been established, and individual patient response and comorbid conditions must often be used to guide drug selection.

2. **Refractory patients:** Approximately 10% to 20% of patients with schizophrenia have an insufficient response to

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first- and second-generation antipsychotics. For these patients, *clozapine* [KLOE-za-peen] has shown to be an effective antipsychotic with a minimal risk of EPS. However, due to the risk of serious adverse effects, its clinical use is limited to refractory patients or patients with substantial risk of suicide or history of suicide attempts. *Clozapine* can produce bone marrow suppression, seizures, and cardiovascular side effects, such as orthostasis. The risk of severe agranulocytosis necessitates frequent monitoring of white blood cell counts. It can also cause constipation that can progress to serious bowel complications.

C. Mechanism of action

1.Dopamine antagonism: All of the first-generation and most of the second-generation antipsychotic drugs block D_2 dopamine receptors in the brain and the periphery (Figure 18.2).

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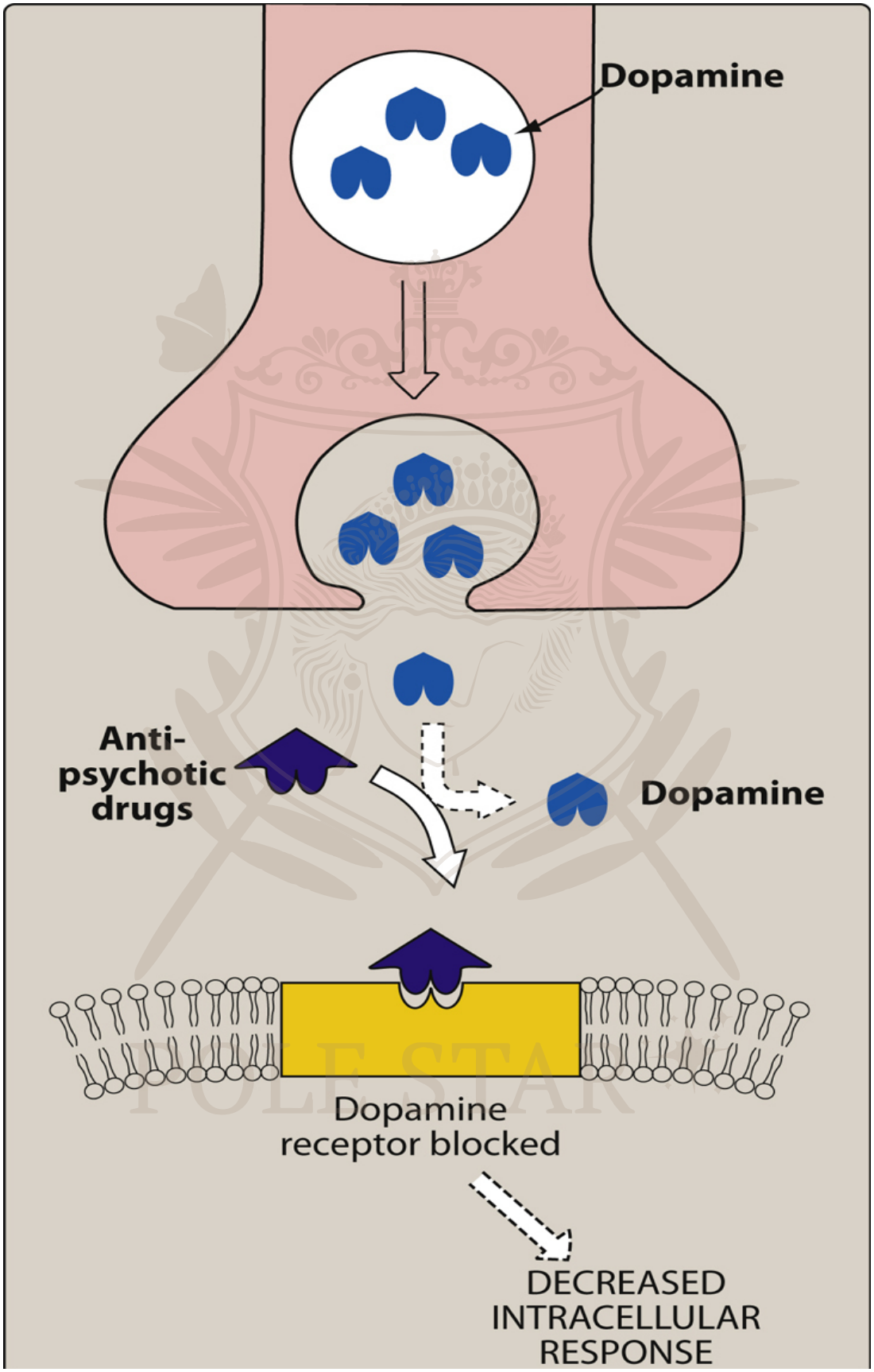
Dopamine
Anti-
psychotic
drugs
Dopamine
Dopamine
receptor blocked
DECREASED
INTRACELLULAR
RESPONSE

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Figure 18.2 Dopamine-blocking actions of antipsychotic drugs.

2.Serotonin receptor–blocking activity: Most of the second-generation agents exert part of their action through antagonism of serotonin receptors (5-HT), particularly 5-HT_{2A} receptors. *Clozapine* has a higher affinity for D_1, D_4, 5-HT_2, muscarinic, and α-adrenergic receptors, but it is also a weak dopamine D_2 receptor antagonist (Figure 18.3). *Risperidone* [ris-PER-ih-dohn] blocks 5-HT_{2A} receptors to a greater extent than it does D_2 receptors, as does *olanzapine* [oh-LANZ-ah-peen]. The second-generation antipsychotics *aripiprazole* [a-rih-PIP-ra-zole], *brexpiprazole* [brex-PIP-ra-zole], and *cariprazine* [kar-IP-ra-zeen] are partial agonists at D_2 and 5-HT_{1A} receptors, as well as antagonists of 5-HT_{2A} receptors. *Quetiapine* [qwe-TY-uh-peen] is relatively weak at blockade of D_2 and 5-HT_{2A} receptors. Its low risk for EPS may also be related to the relatively short period of time it binds to the D_2 receptor. *Pimavanserin* [pim-a-VAN-ser-in] appears to act as an inverse agonist and antagonist at the 5-HT_{2A} receptor and the 5-HT_{2C} receptor, with no appreciable affinity for dopamine receptors. *Pimavanserin* is only indicated for psychosis associated with Parkinson disease.

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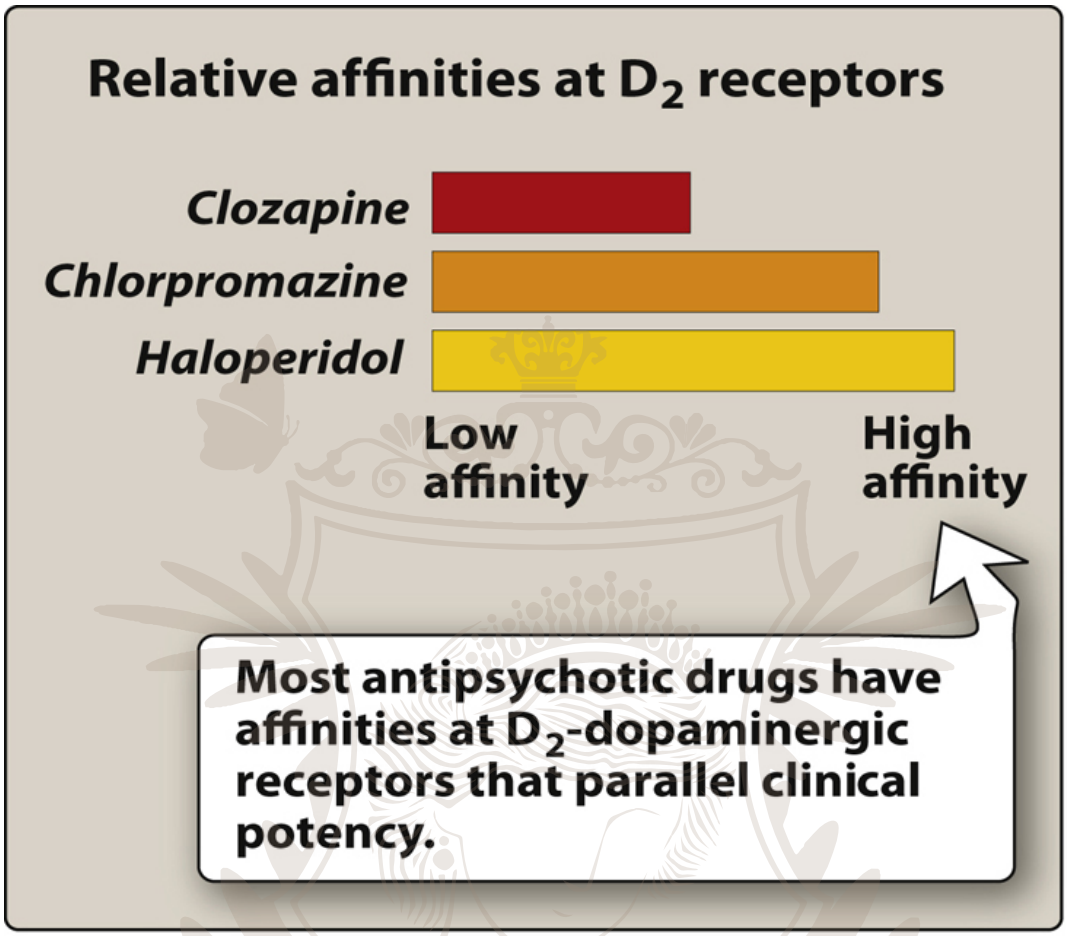

Figure 18.3 Relative affinities of *clozapine*, *chlorpromazine*, and *haloperidol* at D_2 dopaminergic receptors.

D. Actions

The clinical effects of antipsychotic drugs reflect a blockade at dopamine and/or serotonin receptors. However, many antipsychotic agents also block cholinergic, adrenergic, and histaminergic receptors (Figure 18.4). It is unknown what role, if any, these actions have in alleviating the symptoms of psychosis. However, the undesirable adverse effects of antipsychotic drugs often result from pharmacological actions at these other receptors.

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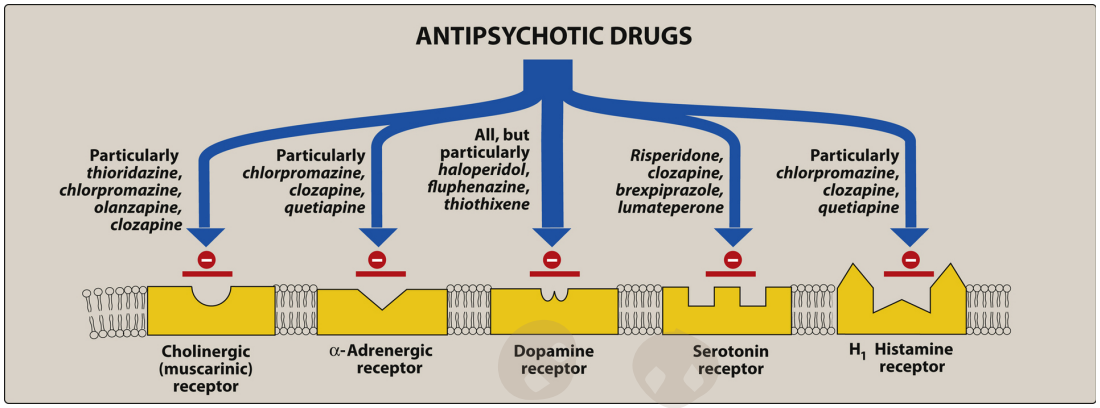

Figure 18.4 Antipsychotic drugs block dopaminergic and serotonergic receptors as well as adrenergic, cholinergic, and histamine-binding receptors.

1.Antipsychotic effects: All antipsychotic drugs can reduce hallucinations and delusions associated with schizophrenia (known as "positive" symptoms) by blocking D_2 receptors in the mesolimbic system of the brain. The "negative" symptoms, such as blunted affect, apathy, and impaired attention, as well as cognitive impairment, are not as responsive to therapy, particularly with the first-generation antipsychotics. Several second-generation agents (for example, *clozapine*) can ameliorate the negative symptoms to some extent. In many cases, other clinical manifestations related to schizophrenia, such as cognitive impairment and anxiety, are the most difficult to treat.

2.Antiemetic effects: The antipsychotic drugs have antiemetic effects that are mediated by blocking D_2 receptors of the chemoreceptor trigger zone of the medulla (see Chapter 42). Figure 18.5 summarizes the antiemetic uses of antipsychotic agents, as well as other drugs used to manage nausea.

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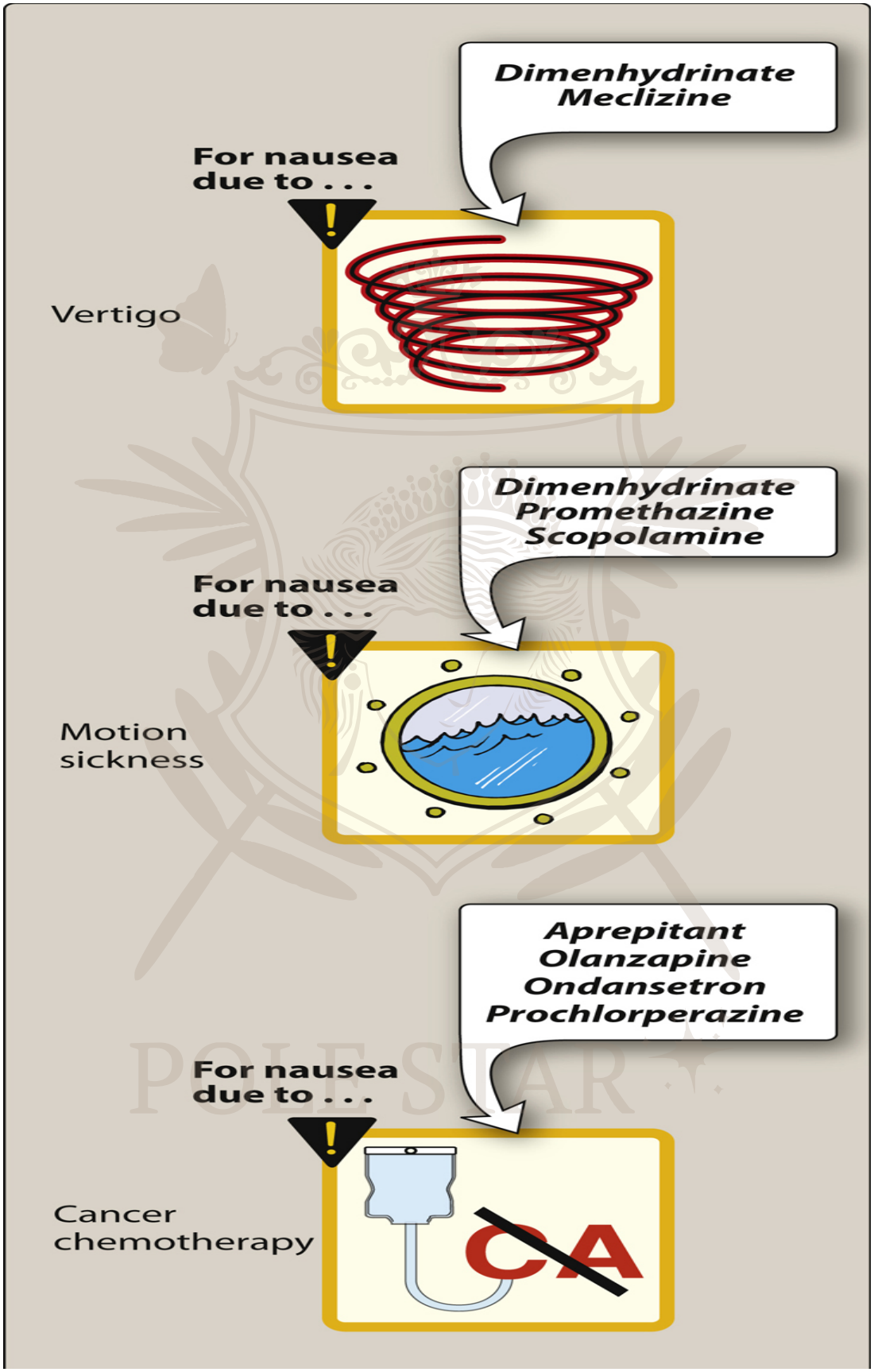
Dimenhydrinate
Meclizine
For nausea due to . . .
Vertigo
Dimenhydrinate
Promethazine
Scopolamine
For nausea due to . . .
Motion sickness
Aprepitant
Olanzapine
Ondansetron
Prochlorperazine
For nausea due to . . .
Cancer chemotherapy
CA

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Figure 18.5 Therapeutic application of antiemetic agents.

E. Therapeutic uses

1.Treatment of schizophrenia: The antipsychotics are the only efficacious pharmacological treatment for schizophrenia. The first-generation antipsychotics are generally most effective in treating the positive symptoms of schizophrenia. The atypical antipsychotics with 5-HT_{2A} receptor–blocking activity may be effective in many patients who are resistant to the traditional agents, especially in treating the negative symptoms of schizophrenia.

2.Prevention of nausea and vomiting: The older antipsychotics (most commonly, *prochlorperazine* [PROE-klor-PER-a-zeen]) are useful in the treatment of drug-induced nausea. In addition, *olanzapine*, an SGA, may be effective for the prevention of both acute and delayed nausea and vomiting due to chemotherapy.

3.Other uses: The antipsychotic drugs can be used as tranquilizers to manage agitated and disruptive behavior secondary to other disorders. *Risperidone* and *aripiprazole* are approved for the management of disruptive behavior and irritability secondary to autism. *Pimozide* [PIM-oh-zide] is primarily indicated for treatment of the motor and phonic tics of Tourette disorder. However, *risperidone* and *haloperidol* are also commonly prescribed for this tic disorder. Many antipsychotic agents are approved for the management of the manic and mixed symptoms associated with bipolar disorder. *Lurasidone* [loo-RAS-i-done], *cariprazine*, and *quetiapine* are indicated for the treatment of bipolar depression. *Paliperidone* [pal-ee-PER-i-dohn] is approved for the treatment of schizoaffective disorder. Some antipsychotics (*aripiprazole*,

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brexpiprazole, and *quetiapine*) are used as adjunctive agents with antidepressants for treatment-refractory depression.

Chlorpromazine has long been used to treat intractable hiccups, although *baclofen* and *gabapentin* are now preferred for this indication.

F. Absorption and metabolism

After oral administration, the antipsychotics show variable absorption that is unaffected by food (except for *ziprasidone* [zi-PRAS-i-done], *lurasidone*, and *paliperidone*, the absorption of which is increased with food). These agents readily pass into the brain and have a large volume of distribution. They are metabolized to many different metabolites, usually by the cytochrome P-450 system in the liver, particularly the CYP2D6, CYP1A2, and CYP3A4 isoenzymes. Some metabolites are active and have been developed as pharmacological agents themselves (for example, *paliperidone* is the active metabolite of *risperidone*, and the antidepressant *amoxapine* is the active metabolite of *loxapine*). Drug interactions must be considered with these agents, since many antipsychotics use the CYP450 enzyme system for metabolism. In addition, smoking can cause CYP1A2 induction and may decrease the levels of certain antipsychotics, such as *clozapine* and *olanzapine*.

Asenapine is available as a sublingual and a transdermal delivery system. *Fluphenazine decanoate*, *haloperidol decanoate*, *risperidone microspheres*, *risperidone suspension*, *paliperidone palmitate*, *aripiprazole monohydrate*, *aripiprazole lauroxil*, and *olanzapine pamoate* are long-acting injectable (LAI) formulations of antipsychotics. These formulations usually have a therapeutic duration of action of 2 to 4 weeks, with some having a duration of 6 to 12 weeks, and the newest formulation of *paliperidone palmitate* can be given every 6 months. Therefore, these LAI formulations are often used to treat outpatients and individuals who are nonadherent with oral medications. Most LAIs are administered as an intramuscular injection; however, two

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formulations, *risperidone suspension* and *fluphenazine decanoate*, may be given as subcutaneous injections.

Clinical Application 18.1: Challenges to Adherence With Antipsychotic Treatment

Adherence to antipsychotic treatment can be challenging to patients for many reasons including poor insight into the illness, denial of the illness, cognitive impairments such as memory, adverse event profiles of the antipsychotics, and stigma of the illness. The use of LAI antipsychotics may not prevent all aspects of nonadherence; however, using these agents can improve the clinician's knowledge of compliance. If the patient misses scheduled appointments, then the treatment team can act to address these issues, rather than assuming that patients are taking the oral antipsychotics as prescribed.

G. Adverse effects

Adverse effects of the antipsychotic drugs can occur in practically all patients and are clinically significant in about 80% (Figure 18.6).

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Figure 18.6 Adverse effects observed in individuals treated with antipsychotic drugs.

1.Extrapyramidal symptoms: The inhibitory effects of dopaminergic neurons are normally balanced by the excitatory actions of cholinergic neurons in the striatum. Blocking dopamine receptors alters this balance, causing a relative excess of cholinergic influence, which results in extrapyramidal motor effects. Specifically, blockade of dopamine receptors in the nigrostriatal pathway is believed to cause these EPS. Dystonias (sustained contraction of muscles leading to twisting, distorted postures), Parkinson-like symptoms, and akathisia (motor restlessness) can occur with both acute and chronic treatment with antipsychotics. The appearance of the movement disorders is generally time- and dose dependent, with dystonias occurring within a few hours to days of treatment, followed by akathisias occurring within days to weeks. Akathisias may also be related to serotonin antagonism and secondary changes in norepinephrine activity, as this often presents as a nervousness or restlessness. Parkinson-like symptoms of bradykinesia, rigidity, and tremor usually occur within weeks to months of initiating treatment. A newer SGA, *lumateperone* [LOO-ma-TE-per-one], has demonstrated a very low incidence of EPS. This is likely because it is much more potent at blocking serotonin than dopamine receptors.

If cholinergic activity is also blocked, a new, more nearly normal balance is restored, and extrapyramidal effects are minimized. This can be achieved by administration of an anticholinergic drug, such as *benztropine* [BENZ-troe-peen]. The therapeutic trade-off is a lower incidence of EPS in exchange for the adverse effect of muscarinic receptor blockade. Akathisia may respond better to β-blockers (for example, *propranolol*) or benzodiazepines, rather than anticholinergic medications.

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2.Tardive dyskinesia: Long-term treatment with antipsychotics can cause tardive dyskinesia (involuntary movements, usually of the tongue, lips, neck, trunk, and limbs). Patients display involuntary movements, including bilateral and facial jaw movements and “fly-catching” motions of the tongue. Tardive dyskinesia can occur after months or years of treatment with antipsychotics and may be irreversible. [Note: The second-generation antipsychotics exhibit a lower incidence of EPS and tardive dyskinesia.] A prolonged holiday from antipsychotics may cause the symptoms to diminish or disappear within a few months. However, in many individuals, tardive dyskinesia is irreversible and persists after discontinuation of antipsychotic therapy. Tardive dyskinesia is postulated to result from an increased number of dopamine receptors that are synthesized as a compensatory response to long-term dopamine receptor blockade. This makes the neuron supersensitive to the actions of dopamine, and it allows the dopaminergic input to this structure to overpower the cholinergic input, causing excess movement in the patient. Traditional anti-EPS medications, such as the anticholinergic treatment *benztropine*, may actually worsen tardive dyskinesia. *Valbenazine* [val-BEN-a-zeen] and *deutetrabenazine* [doo-TET-ra-BEN-a-zeen] are inhibitors of the vesicular monoamine transporter, and they are indicated for the management of tardive dyskinesia. These agents cause a decreased uptake of monoamines into synaptic vesicles and depletion of monoamine stores, ideally focused on dopamine, to address the symptoms of tardive dyskinesia.

3.Neuroleptic malignant syndrome: This rare but potentially fatal reaction to antipsychotic drugs is characterized by muscle rigidity, fever, altered mental status and stupor, autonomic instability (unstable blood pressure, tachycardia, tachypnea, diaphoresis), and myoglobinemia. Treatment necessitates discontinuation of the antipsychotic agent and supportive therapy. Administration of *dantrolene*, a skeletal

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muscle relaxant, or *bromocriptine*, a dopamine agonist, may be helpful.

4.Anticholinergic effects: Some of the antipsychotics, particularly *thioridazine* [THYE-oh-RID-a-zeen], *chlorpromazine*, *clozapine*, and *olanzapine*, produce anticholinergic effects. These effects include blurred vision, dry mouth (the exception is *clozapine*, which increases salivation), confusion, and inhibition of gastrointestinal and urinary tract smooth muscle, leading to constipation and urinary retention. The anticholinergic effects may actually assist in reducing the risk of EPS with these agents.

5.Other effects: Drowsiness occurs during the first few weeks of treatment. Blockade of α-adrenergic receptors with some agents (for example, *chlorpromazine* and *clozapine*) can cause orthostatic hypotension and light-headedness. Sedation occurs with those drugs that are potent antagonists of the H_1-histamine receptor, including *chlorpromazine*, *olanzapine*, *quetiapine*, and *clozapine.* The antipsychotics also alter temperature-regulating mechanisms and can produce poikilothermia (condition in which body temperature varies with the environment). In the pituitary, antipsychotics that block D_2 receptors in the dopaminergic tuberoinfundibular pathway (for example, *risperidone* and *paliperidone*) may cause an increase in prolactin release, which can cause adverse effects such as gynecomastia, amenorrhea, or galactorrhea. Sexual dysfunction may occur with the antipsychotics due to various receptor-binding characteristics. Weight gain is also a common adverse effect of antipsychotics and is more significant with the second-generation agents. Significant weight gain is often a reason for nonadherence. [Note: A combination of *olanzapine* and *samidorphan* [SAM-i-dor-fan] (an opioid receptor antagonist) was developed to lessen weight gain normally observed with *olanzapine.* This combination is contraindicated in patients receiving opioids, due to the ability

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of *samidorphan* to induce opioid withdrawal.] Glucose and lipid profiles should be monitored in patients taking antipsychotics, as the second-generation agents may increase these laboratory parameters and possibly exacerbate preexisting diabetes or hyperlipidemia. Some antipsychotics have been associated with mild to significant QT prolongation. *Thioridazine* has the highest risk, and *ziprasidone* and *iloperidone* [eye-low-PER-ee-dohn] also have cautions with their use due to this effect. Other antipsychotics have a general precaution regarding QT prolongation, even if the risk is relatively low.

6. **Cautions and contraindications:** All antipsychotics may lower the seizure threshold and should be used cautiously in patients with seizure disorders or those with an increased risk for seizures, such as withdrawal from alcohol. These agents also carry the warning of increased risk for mortality when used in elderly patients with dementia-related behavioral disturbances and psychosis. In elderly patients, antipsychotic agents should be initiated at a lower dose and titrated more slowly. Patients with mood disorders treated with antipsychotic therapy should be monitored for worsening of mood and suicidal ideation or behaviors.

H. Maintenance treatment

Patients who have had two or more psychotic episodes secondary to schizophrenia should receive maintenance therapy for at least 5 years, and some experts prefer indefinite therapy. The rate of relapse may be lower with second-generation drugs over FGAs (Figure 18.7), and the relapse rates with LAIs may be lower than with oral agents. Figure 18.8 summarizes the properties and therapeutic uses of some of the antipsychotic drugs.

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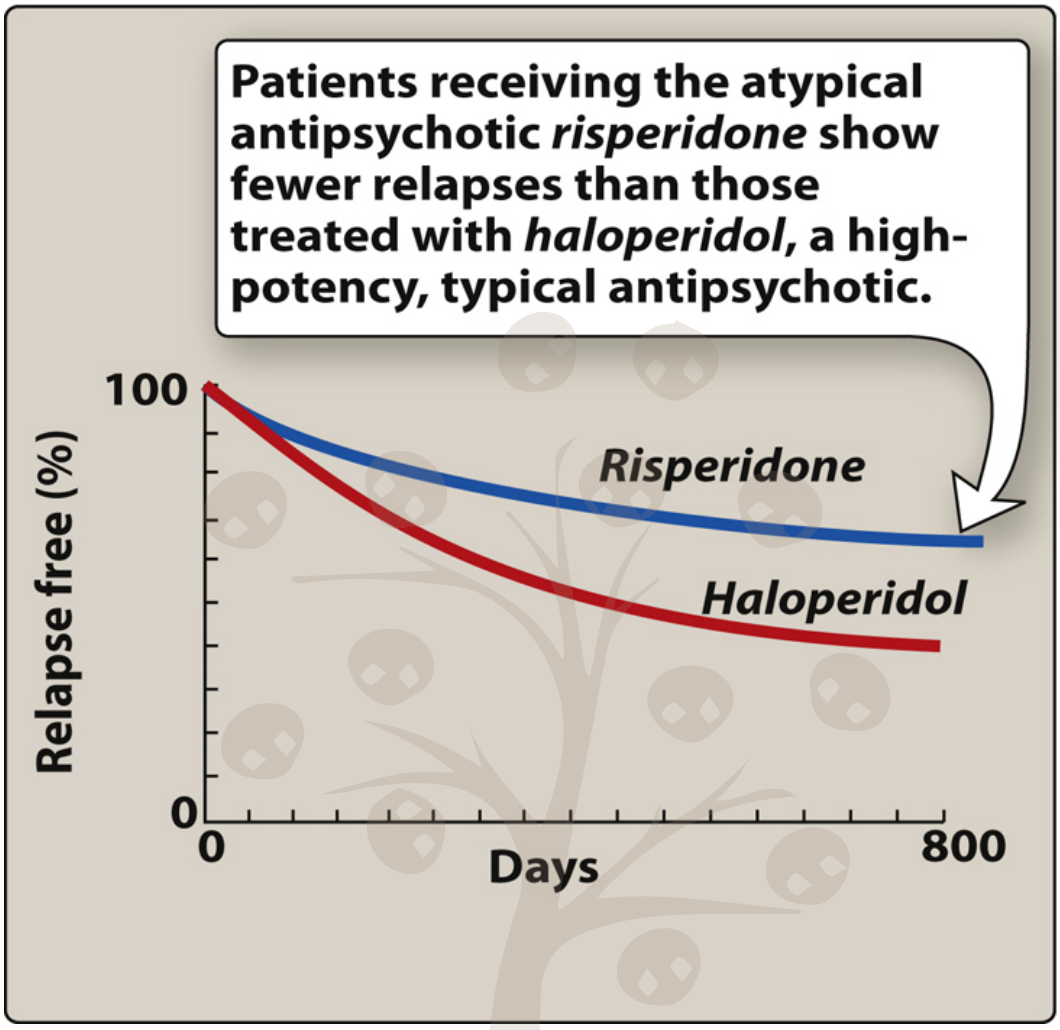

Figure 18.7 Rates of relapse among patients with schizophrenia after maintenance therapy with either *risperidone* or *haloperidol*.

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DRUG NAME	INDICATIONS	SEDATION	EPS	ANTI-CHOLINERGIC	ORTHOSTASIS	THERAPEUTIC NOTES & SPECIAL SIDE EFFECTS
First generation						
Chlorpromazine	Psychosis, mania, N/V, intractable hiccups	++++	+++	+++	++++	
Fluphenazine	Schizophrenia	+	++++	+	+	LAI for patients with a history of nonadherence with oral regimens
Haloperidol	Schizophrenia, Tourette syndrome, severe behavior problems in children	+	++++	0	+	LAI for patients with a history of nonadherence with oral regimens; low potential for weight gain
Loxapine	Schizophrenia	+++	+++	++	++	Metabolite is *amoxapine* (antidepressant)
Molindone	Schizophrenia	+	+++	++	++	Weight loss
Perphenazine	Schizophrenia, N/V	++	+++	++	++	
Prochlorperazine	Schizophrenia, anxiety, N/V	++	+++	+	+	IM and suppository formulation available; commonly used for N/V
Thioridazine	Schizophrenia	++++	++	++++	++++	QTc interval prolongation - avoid in combination with other drugs known to prolong the QTc interval and in patients with congenital long QT syndrome or a history of cardiac arrhythmias; pigmentary retinopathy
Thiothixene	Schizophrenia	+	+++	+	+	
Trifluoperazine	Schizophrenia, anxiety	++	+++	++	++	
Second generation						
Aripiprazole	Schizophrenia, bipolar mania, irritability secondary to autistic disorder, adjunctive treatment of MDD, bipolar maintenance	+	+	0	+	Two LAI formulations available; N/V likely due to D_2 partial agonism; low risk for prolactin-related problems
Asenapine	Schizophrenia, acute mania	++	++	0	+	Transdermal and SL formulation available; dysgeusia and oral hypoesthesia with SL formulation; low potential for weight gain
Brexpiprazole	Schizophrenia, adjunctive treatment of MDD	+	+	0	+	N/V likely due to D_2 partial agonism; low risk for prolactin-related problems; low potential for weight gain
Cariprazine	Schizophrenia, bipolar mania, bipolar depression	+	++	0	0	N/V likely due to D_2 partial agonism; low risk for prolactin-related problems; low potential for weight gain
Clozapine	Treatment-resistant schizophrenia, recurrent suicidal behavior in schizophrenia or schizoaffective disorder	++++	–/+	++++	++++	High risk for blood dyscrasias, orthostasis, seizures, weight gain, sialorrhea; myocarditis
Iloperidone	Schizophrenia	+	+	+	++	QTc interval prolongation
Lumateperone	Schizophrenia	++	–/+	0	+	Low potential for weight gain
Lurasidone	Schizophrenia, bipolar depression	+	+	0	+	Food increases absorption; low potential for weight gain
Olanzapine	Schizophrenia, bipolar mania	+++	++	++	++	LAI formulation available; high potential for weight gain
Paliperidone	Schizophrenia, schizoaffective disorder	+	+	0	++	LAI formulation available; high risk for increase in prolactin level; active metabolite of *risperidone*
Quetiapine	Schizophrenia, acute mania, bipolar depression, adjunctive treatment of MDD	+++	+	+	++	High potential for weight gain
Risperidone	Schizophrenia, acute mania, irritability secondary to autistic disorder, bipolar maintenance	+	++	0	++	LAI formulation available; high risk for increase in prolactin level; moderate potential for weight gain
Ziprasidone	Schizophrenia, bipolar mania	+	+	0	+	Contraindicated in patients with a known history of QT prolongation, a recent acute myocardial infarction, and with uncompensated heart failure; low potential for weight gain

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Figure 18.8 Summary of antipsychotic agents commonly used to treat schizophrenia.EPS = extrapyramidal effects; IM = intramuscular; LAI = long-acting injectable; MDD = major depressive disorder; N/V = nausea and vomiting; SL = sublingual.

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Chapter Summary

- The clinical effects of antipsychotic drugs reflect a blockade at dopamine and/or serotonin receptors. However, many antipsychotic agents also block cholinergic, adrenergic, and histaminergic receptors, leading to the potential for numerous adverse effects.
- The antipsychotic effects of the first-generation antipsychotic drugs (FGAs) reflect their competitive blockade of dopamine D_2 receptors.
- The second-generation antipsychotic drugs (SGAs) cause a blockade of both serotonin 5-HT_2 and dopamine D_2 receptors. *Aripiprazole*, *brexpiprazole*, and *cariprazine* are SGAs that exert their therapeutic effects due to D_2 receptor partial agonism and $5HT_{2A}$ receptor antagonism.
- All antipsychotic drugs can reduce hallucinations and delusions associated with schizophrenia (known as "positive" symptoms) by blocking D_2 receptors in the mesolimbic system of the brain. The "negative" symptoms, such as blunted affect, apathy, and impaired attention are not as responsive to therapy. While the FGAs only help alleviate positive symptoms, the SGAs can help alleviate positive and negative symptoms.
- The FGAs are more likely to be associated with movement disorders known as extrapyramidal symptoms (EPS), particularly drugs that bind tightly to dopaminergic neuroreceptors, such as *haloperidol.* Movement disorders are somewhat less likely with medications that bind less potently, such as *chlorpromazine.*
- The SGAs have a lower incidence of EPS than the FGAs but are associated with a higher risk of metabolic adverse effects, such as diabetes, hypercholesterolemia, and weight gain.
- In general, antipsychotics are considered equally effective. Therefore, agents should be selected based on patient-specific factors. Alternative dosage forms may improve adherence to treatment and change adverse-event profiles for some agents.
- Antipsychotic drugs may also be used for other indications, such as mania, irritability, agitation, anxiety, and refractory mood symptoms occurring with depression and bipolar disorder.

STUDY QUESTIONS

Choose the ONE best answer.

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18.1 An adolescent boy is newly diagnosed with schizophrenia. Which of the following antipsychotic agents may have the best chance to improve his apathy and blunted affect?

A. Chlorpromazine
B. Fluphenazine
C. Haloperidol
D. Olanzapine

Correct answer = D. While FGAs only help manage the positive symptoms associated with schizophrenia, the second-generation antipsychotics can help with the positive and negative symptoms. Olanzapine, a second-generation agent, is the only antipsychotic on the provided list that has some reported benefit in improving the negative symptoms of schizophrenia. All of the listed agents have the potential to diminish the hallucinations and delusional thought processes (positive symptoms).

18.2 Which of the following antipsychotics is a partial agonist at the dopamine D_2 receptor?

A. Cariprazine
B. Clozapine
C. Perphenazine
D. Risperidone

Correct answer = A. Cariprazine is the only agent listed that acts as a partial agonist at D_2 receptors. Theoretically, the drug enhances action at these receptors under low dopamine conditions and blocks activation when dopamine levels are high. All of the other drugs are antagonistic at D_2 receptors.

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18.3 A 21-year-old man recently began pimozide therapy for Tourette disorder. He has been experiencing "different-appearing tics," such as prolonged contraction of the facial muscles and opisthotonos (extrapyramidal spasm of the body in which the head and heels are bent backward and the body is bowed forward). Which of the following drugs would be beneficial in reducing these symptoms?

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A. Benztropine
B. Bromocriptine
C. Prochlorperazine
D. Risperidone

Correct answer = A. The patient is experiencing extrapyramidal symptoms (EPS) due to pimozide; therefore, a muscarinic antagonist such as benztropine would be effective in reducing the symptoms. The other drugs would have no effect or, in the case of prochlorperazine and risperidone, might worsen the adverse symptoms.

18.4 A 26-year-old woman is started on a new antipsychotic agent for the treatment of acute mania related to bipolar disorder. At her follow-up appointment, she complains that she is very tired due to the sedating effects of the medication. Which of the following antipsychotics was most likely prescribed?

A. Fluphenazine
B. Thiothixene
C. Quetiapine
D. Haloperidol

Correct answer = C. Quetiapine has strong antihistaminergic effects causing sedation, and it is sometimes used at low doses as a sedative–hypnotic, even though this use is considered off-label. The other antipsychotic agents listed are weaker at blocking the histamine receptor and, therefore, are not as sedating.

18.5 A 30-year-old man is treated with haloperidol for schizophrenia. His psychosis is well managed with haloperidol; however, he is reporting restlessness and the inability to sit still at the dinner table. He also states that his family notices that he frequently paces the hallway. Which of the following is the best agent to treat these symptoms?

A. Benztropine
B. Dantrolene

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C. Bromocriptine
D. Propranolol

Correct answer = D. The symptoms are consistent with akathisia (restlessness). Propranolol, a β-blocker, is considered the drug of choice for the management of antipsychotic-induced akathisia. Benztropine is more effective for pseudoparkinsonism and acute dystonias. Bromocriptine is more effective for Parkinson-like symptoms, and dantrolene is a muscle relaxant that is best-reserved for managing some symptoms of neuroleptic malignant syndrome.

18.6 A 33-year-old man with a history of treatment-resistant schizophrenia presents for routine monitoring of absolute neutrophil count, as the medication he was prescribed can cause severe neutropenia or agranulocytosis. Which medication is the patient most likely taking?

A. Risperidone
B. Olanzapine
C. Lithium
D. Clozapine

Correct answer = D. Clozapine is the only antipsychotic medication that has a boxed warning and a significant risk of agranulocytosis in approximately 1% of patients. This requires regular monitoring of white blood cell counts. In addition, patients should be asked to report symptoms related to an infection, such as fever, sore throat, or lethargy. Although other antipsychotics have case reports of blood dyscrasias and a general warning for such issues, clozapine is considered to have the highest risk and is only available through a special prescribing program.

18.7 A 6-year-old boy is diagnosed with autism spectrum disorder and exhibits significant irritability and combativeness, which impairs successful implementation and benefit from occupational and speech therapies. Which of the following treatments is approved for the management of these behaviors?

A. Trifluoperazine

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B. Lumateperone
C. Olanzapine
D. Aripiprazole

Correct answer = D. Of the antipsychotic drugs listed, only aripiprazole is approved for the treatment of these disruptive behaviors that impair nonpharmacological interventions. Risperidone is also approved for such use. Although other antipsychotics may treat these symptoms, they have not demonstrated, or proven, the efficacy and safety to the extent that aripiprazole and risperidone have.

18.8 A person diagnosed with bipolar disorder and struggling with adherence to oral medications is started on a long-acting injectable antipsychotic to prevent relapse of manic episodes. Which of the following antipsychotics is most likely prescribed?

A. Quetiapine
B. Risperidone
C. Chlorpromazine
D. Lurasidone

Correct answer = B. Of the antipsychotics listed, each one is approved for use in either the manic or depressed episodes of bipolar. However, only risperidone is available as extended-release microspheres in a long-acting injectable (LAI) formulation approved for the maintenance and relapse reduction of mood episodes related to bipolar disorder. The aripiprazole monohydrate LAI is also-indicated for this use.

18.9 A 25-year-old man with schizophrenia is experiencing the extrapyramidal symptoms (EPS) of dystonic reactions in his arms and shoulders from perphenazine. He is now being considered for a switch to an antipsychotic with a lower risk of EPS. Which of the following agents is the most appropriate choice for this patient?

A. Quetiapine
B. Haloperidol

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C. Trifluoperazine
D. Fluphenazine

Correct answer = A. Of the antipsychotics listed, only quetiapine is a second-generation antipsychotic (SGA) and considered to have a low risk for EPS. The other drugs listed are all first-generation agents and are more potent at blocking the D_2 receptor than perphenazine, and, thus, are expected to have a higher risk for EPS than perphenazine.

18.10 A 34-year-old woman has been struggling with refractory depression only partially responsive to multiple trials of various antidepressant drugs. She is a candidate for adjunctive treatment of her depression with a second-generation antipsychotic (SGA) for augmentation of the antidepressant response. Which of the following SGAs would be most appropriate as adjunctive treatment in refractory depression for this patient?

A. Paliperidone
B. Risperidone
C. Brexpiprazole
D. Iloperidone

Correct answer = C. Brexpiprazole is the only listed agent that is approved as an adjunctive treatment to antidepressant therapy for refractory depression. Although the other agents may have benefit in such a population, their efficacy and safety are not as well documented and established and thus are unapproved for such use.

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19

Drugs for Epilepsy

Jeannine M. Conway, Angela K. Birnbaum

I. OVERVIEW

Approximately 10% of the population has at least one seizure in their lifetime. Globally, epilepsy is the fourth most common neurologic disorder after migraine, cerebrovascular disease (stroke), and Alzheimer disease. Epilepsy is not a single entity but an assortment of different seizure types and syndromes originating from several mechanisms that have in common the sudden, excessive, and synchronous discharge of cerebral neurons. This abnormal electrical activity may result in a variety of events, including loss of consciousness, abnormal movements, atypical or odd behavior, and distorted perceptions that are of limited duration but recur if untreated. The site of origin of abnormal neuronal firing determines the symptoms that occur. For example, if the motor cortex is involved, the patient may experience abnormal movements or a generalized convulsion. Seizures originating in the parietal or occipital lobe may include visual, auditory, and olfactory hallucinations. Medications are the most widely used mode of treatment of patients with epilepsy. In general, seizures can be controlled with one medication in approximately 75% of patients. Other patients may require more than one medication in order to optimize seizure control, and some patients may never obtain total seizure control. A summary of antiseizure medications is shown in Figure 19.1.

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Figure 19.1 Summary of agents used in the treatment of epilepsy.

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II. ETIOLOGY OF SEIZURES

Epilepsy can be due to an underlying genetic, structural, or metabolic cause or an unknown etiology. In most cases, epilepsy has no identifiable cause. The neuronal discharge in epilepsy results from firing of a small population of neurons in a specific area of the brain referred to as the "primary focus." Focal areas that are functionally abnormal may be triggered into activity by changes in physiologic factors, such as an alteration in blood gases, pH, electrolytes, and blood glucose and changes in environmental factors, such as sleep deprivation, alcohol intake, and stress. A number of causes, such as illicit drug use, tumor, head injury, hypoglycemia, meningeal infection, and the rapid withdrawal of alcohol from an alcoholic, can precipitate seizures. In cases when the source of a seizure can be determined and corrected, medication may not be necessary. For example, a seizure that is caused by a drug reaction is not epilepsy and does not require chronic therapy. In other situations, antiseizure medications may be needed when the primary cause of the seizures cannot be corrected. Although multiple specific epilepsy syndromes that include symptoms other than seizures have been classified, a discussion of these syndromes is beyond the scope of this chapter.

III. CLASSIFICATION OF SEIZURES

It is important to correctly classify seizures to determine appropriate treatment. Seizures are categorized by site of origin, etiology, electrophysiologic correlation, and clinical presentation. Nomenclature developed by the International League Against Epilepsy is considered the standard classification for seizures and epilepsy syndromes (Figure 19.2). Seizures are classified into two broad groups: focal and generalized.

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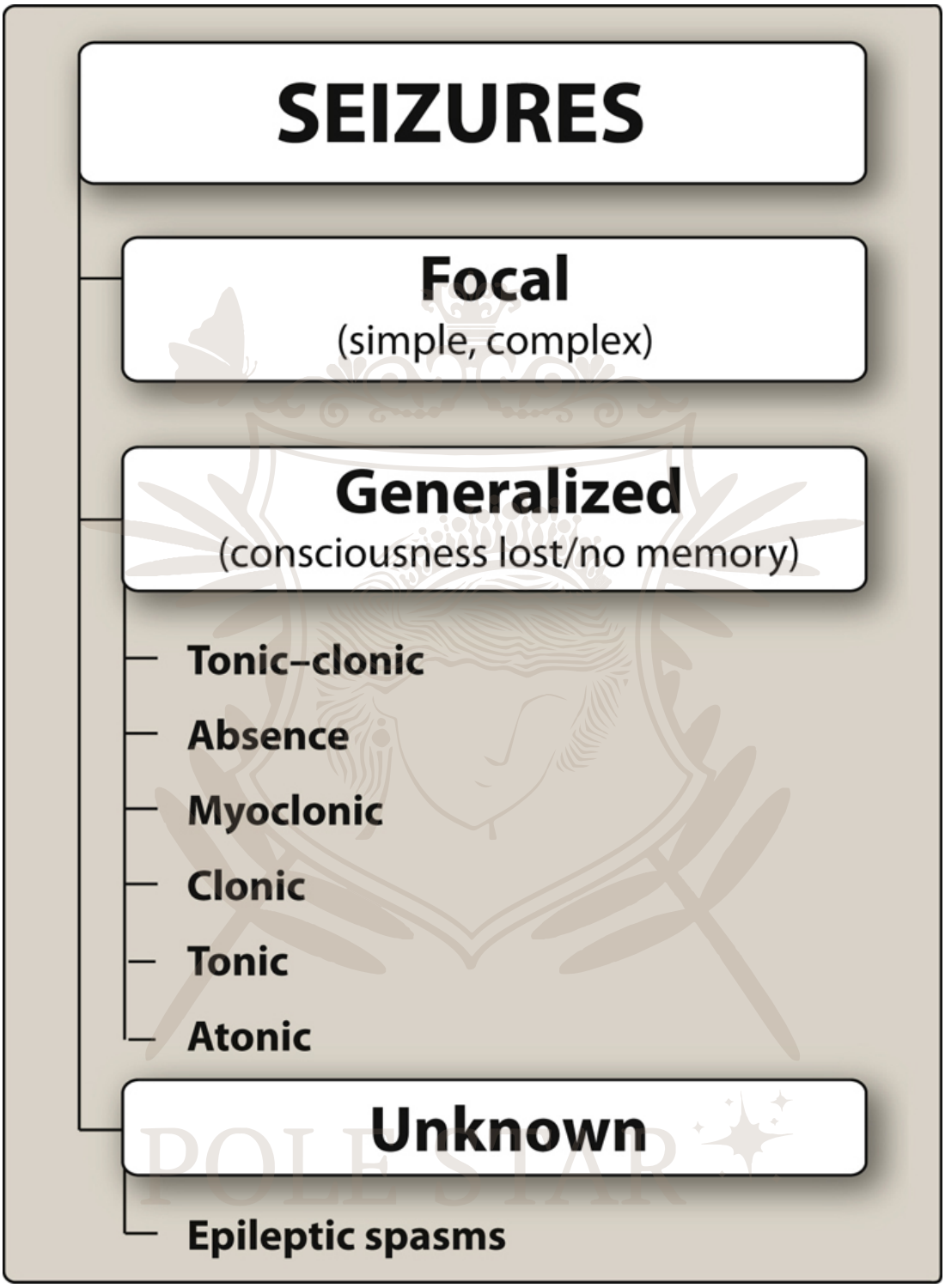

Figure 19.2 Classification of epilepsy.

A. Focal

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Focal seizures involve only a portion of one hemisphere of the brain. The symptoms of each seizure type depend on the site of neuronal discharge and on the extent to which the electrical activity spreads to other neurons in the brain. Focal seizures may progress to become bilateral generalized tonic–clonic seizures. Patients may lose consciousness or awareness. This seizure type may begin with motor or nonmotor activity.

B. Generalized

Generalized seizures may begin locally and then progress to include abnormal electrical discharges throughout both hemispheres of the brain. Primary generalized seizures may be convulsive or nonconvulsive, and the patient usually has an immediate loss of consciousness.

1.Tonic–clonic: These seizures result in loss of consciousness, followed by tonic (continuous contraction) and clonic (rapid contraction and relaxation) phases. The seizure may be followed by a period of confusion and exhaustion due to depletion of glucose and energy stores.

2.Absence: These seizures involve a brief, abrupt, and self-limiting loss of consciousness. The onset generally occurs in patients at 3 to 5 years of age and lasts until puberty or beyond. The patient stares and exhibits rapid eye blinking, which lasts for 3 to 5 seconds. An absence seizure has a very distinct three-per-second spike and wave discharge seen on electroencephalogram.

3.Myoclonic: These seizures consist of short episodes of muscle contractions that may recur for several minutes. They generally occur after wakening and exhibit as brief jerks of the limbs. Myoclonic seizures occur at any age but usually begin around puberty or early adulthood.

4.Clonic: These seizures consist of short episodes of muscle contractions that may closely resemble myoclonic seizures. Consciousness is more impaired with clonic seizures as compared with myoclonic.

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5.Tonic: These seizures involve increased tone in the extension muscles and are generally less than 60 seconds.

6.Atonic: These seizures are also known as drop attacks and are characterized by a sudden loss of muscle tone.

IV. MECHANISM OF ACTION OF ANTISEIZURE MEDICATIONS

Drugs reduce seizures through mechanisms such as blocking voltage-gated channels (Na^+ or Ca^{2+}), enhancing inhibitory γ-aminobutyric acid (GABA)ergic impulses, and interfering with excitatory glutamate transmission. Some antiseizure medications appear to have multiple targets within the central nervous system (CNS), whereas the mechanism of action for some agents is poorly defined. Antiseizure medications suppress seizures but do not “cure” or “prevent” epilepsy.

V. DRUG SELECTION

Choice of drug treatment is based on the classification of the seizures, patient-specific variables (for example, age, comorbid medical conditions, lifestyle, and personal preference), and characteristics of the drug (such as cost and drug interactions). For example, focal-onset seizures are treated with a different set of medications than primary generalized seizures, although the list of effective agents overlaps. The toxicity of the agent and characteristics of the patient are major considerations in drug selection. In newly diagnosed patients, monotherapy is instituted with a single agent until seizures are controlled or toxicity occurs (Figure 19.3). Compared with those receiving combination therapy, patients receiving monotherapy exhibit better medication adherence and fewer side effects. If seizures are not controlled with the first medication, monotherapy with an alternate medication or the addition of medications should be considered (Figure 19.4). Failing that, other medical management (vagal nerve stimulation, surgery, etc.) should be considered. Awareness of the antiseizure medications available and their mechanisms of action, pharmacokinetics, potential for drug–drug interactions, and adverse effects is essential for successful treatment of the patient.

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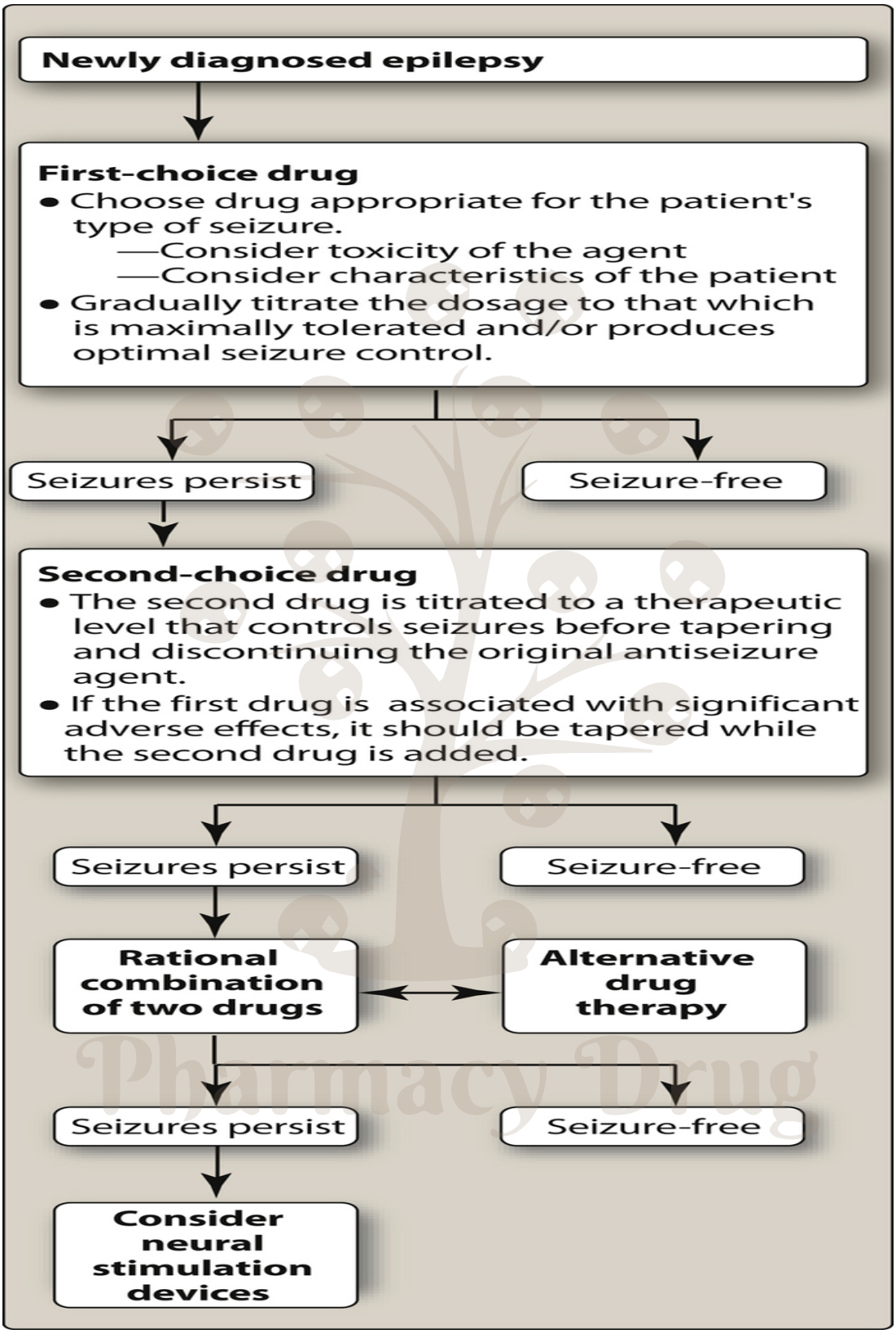

Figure 19.3 Therapeutic strategies for managing newly diagnosed epilepsy.

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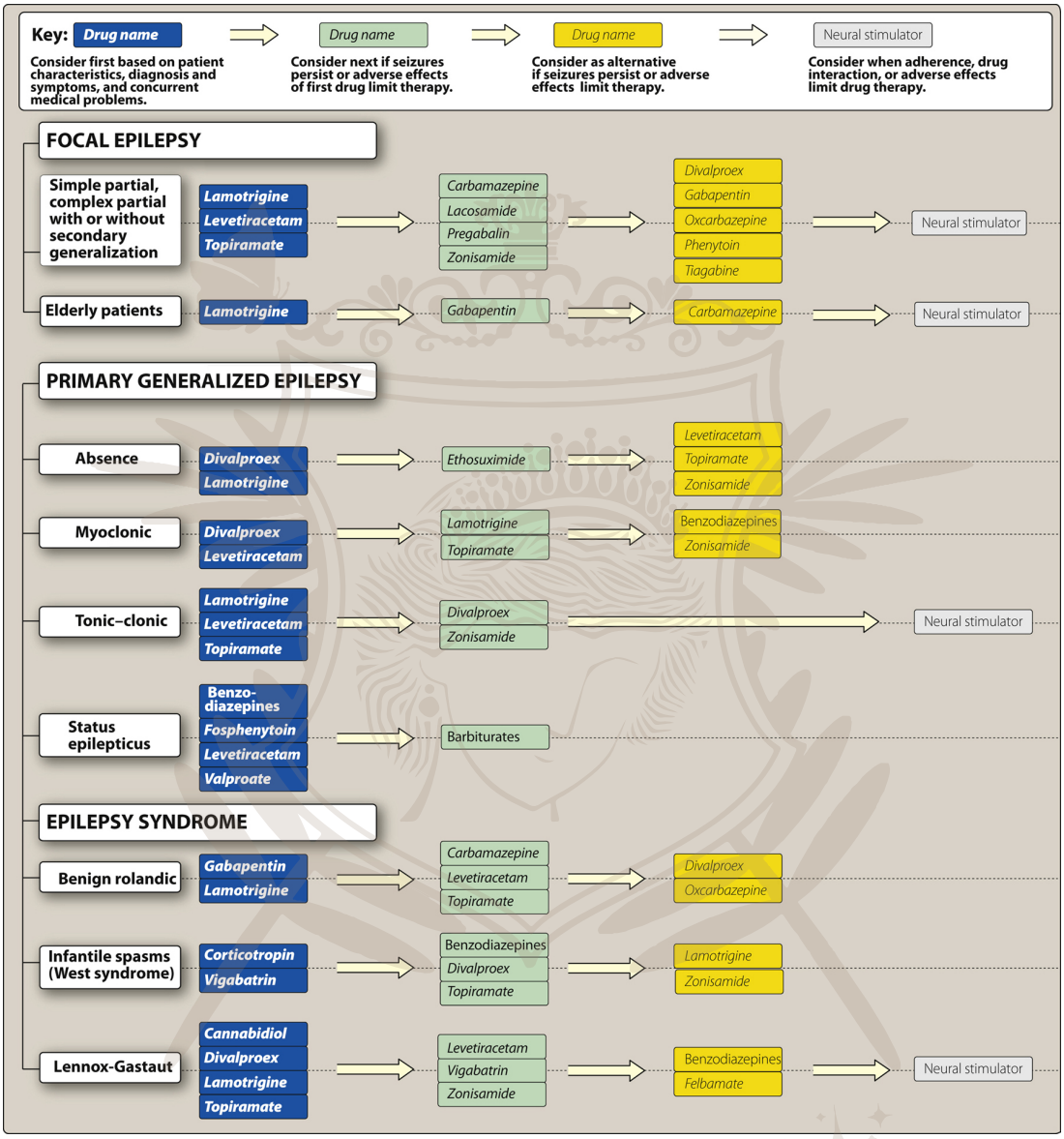

Figure 19.4 Therapeutic indications for antiseizure agents.Benzodiazepines = *diazepam* and *lorazepam*.

VI. ANTISEIZURE MEDICATIONS

Many new antiseizure medications have been approved in the last few decades. Some of these agents are thought to have potential advantages

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over older drugs in terms of pharmacokinetics, tolerability, and reduced risk for drug–drug interactions. However, studies have failed to demonstrate that the newer drugs are significantly more efficacious than older agents. Figure 19.5 summarizes pharmacokinetic properties of the antiseizure medications, and Figure 19.6 shows common adverse effects. Suicidal behavior and suicidal ideation have been identified as a risk with antiseizure medications. In addition, virtually all antiseizure medications have been associated with multiorgan hypersensitivity reactions, a rare idiosyncratic reaction characterized by rash, fever, and systemic organ involvement.

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ANTISEIZURE MEDICATION	PROTEIN BINDING*	HALF-LIFE**	ACTIVE METABOLITE	MAJOR ORGAN OF ELIMINATION	DRUG INTERACTIONS
Brivaracetam	Low	9		Liver	✔
Cannabidiol	High	56–61	7-OH-CBD	Liver	✔
Carbamazepine	Moderate	6–15	CBZ-10,11-epoxide	Liver	✔
Cenobamate	Moderate	50–60		Liver	✔
*Eslicarbazepine acetate^*	Low	8–24	Eslicarbazepine (S-licarbazepine)	Kidney	✔
Ethosuximide	Low	25–26		Liver	✔
Felbamate	Low	20–23		Kidney/Liver	✔
Fenfluramine	Moderate	20		Liver	✔
*Fosphenytoin^*	High	12–60	*Phenytoin*	Liver	✔
Gabapentin	Low	5–9		Kidney	
Lacosamide	Low	13		Various	
Lamotrigine	Low	25–32		Liver	✔
Levetiracetam	Low	6–8		Hydrolysis	
*Oxcarbazepine^*	Low	5–13	Monohydroxy metabolite (MHD)	Liver	✔
Perampanel	High	105		Liver	✔
Phenobarbital	Low	72–124		Liver	✔
Phenytoin	High	12–60		Liver	✔
Pregabalin	Low	5–6.5		Kidney	
Primidone	High	72–124	*Phenobarbital*, PEMA	Liver	✔
Rufinamide	Low	6–10		Liver	✔
Stiripentol	High	4.5–13		Liver	✔
Tiagabine	High	7–9		Liver	✔
Topiramate	Low	21		Various	✔
Valproic acid (Divalproex)	Moderate/ High	6–18	Various	Liver	✔
Vigabatrin	Low	7.5		Kidney	✔
Zonisamide	Low	63		Liver	✔

*Low = 60% or less, moderate = 61%-85%, high = >85%. **Half-life in hours. ^Prodrug. PEMA = phenylethylmalonamide.

Figure 19.5 Summary of the pharmacokinetics of antiseizure medications used as chronic therapy.

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Figure 19.6 Notable adverse effects of antiseizure medications.

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A. Benzodiazepines

Benzodiazepines bind to GABA inhibitory receptors to reduce the firing rate of neurons. Because tolerance can develop with chronic use, most benzodiazepines are reserved for emergency or acute seizure treatment. However, *clonazepam* [kloe-NAY-ze-pam] and *clobazam* [KLOE-ba-zam] may be prescribed for particular types of seizures. *Clobazam* is metabolized via CYP3A4 and 2C19 and has an active metabolite, norclobazam. *Diazepam* [dye-AZ-e-pam] is also available for rectal and intranasal administration to avoid or interrupt prolonged generalized tonic–clonic seizures or clusters when oral administration is not possible.

B. Brivaracetam

Brivaracetam [briv-a-RA-se-tam] is approved for treatment of focal-onset seizures in adults. It demonstrates high and selective affinity for a synaptic vesicle protein (SV2A); however, the exact mechanism of antiseizure action is unknown. The drug is well absorbed after oral administration and metabolized by both hydrolysis and CYP2C19 (minor). Concurrent use of strong CYP450-inducing medications may lead to lower plasma concentrations. *Brivaracetam* is a moderate inhibitor of epoxide hydrolase, resulting in increased levels of the active metabolite of *carbamazepine* when the drugs are coadministered.

C. Cannabidiol

Cannabidiol [KAN-a-bi-DYE-ol] is approved for treatment of seizures due to Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex. The drug is extracted from the *Cannabis sativa* plant, and it is both a substrate and inhibitor of several CYP450 enzymes, resulting in clinically relevant drug interactions. The drug does not have psychoactive effects, and drowsiness, diarrhea, vomiting, and decreased appetite are the most frequent side effects. *Cannabidiol* is only available as a liquid formulated with sesame oil. There is an increased risk of liver enzyme elevation when used with *divalproex*.

D. Carbamazepine

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Carbamazepine [kar-ba-MAZ-a-peen] blocks sodium channels, thereby possibly inhibiting the generation of repetitive action potentials in the epileptic focus and preventing spread. *Carbamazepine* is effective for treatment of focal seizures, generalized tonic–clonic seizures, trigeminal neuralgia, and bipolar disorder. It induces its own metabolism, resulting in lower total *carbamazepine* blood concentrations at higher doses. *Carbamazepine* is an inducer of the CYP1A2, CYP2C, CYP3A, and UDP glucuronosyltransferase (UGT) enzymes, which increases the clearance of other drugs (Figure 19.7). Hyponatremia may be noted in some patients, especially the elderly, and may necessitate a change in medication. *Carbamazepine* should not be prescribed for patients with absence seizures because it may cause an increase in seizures.

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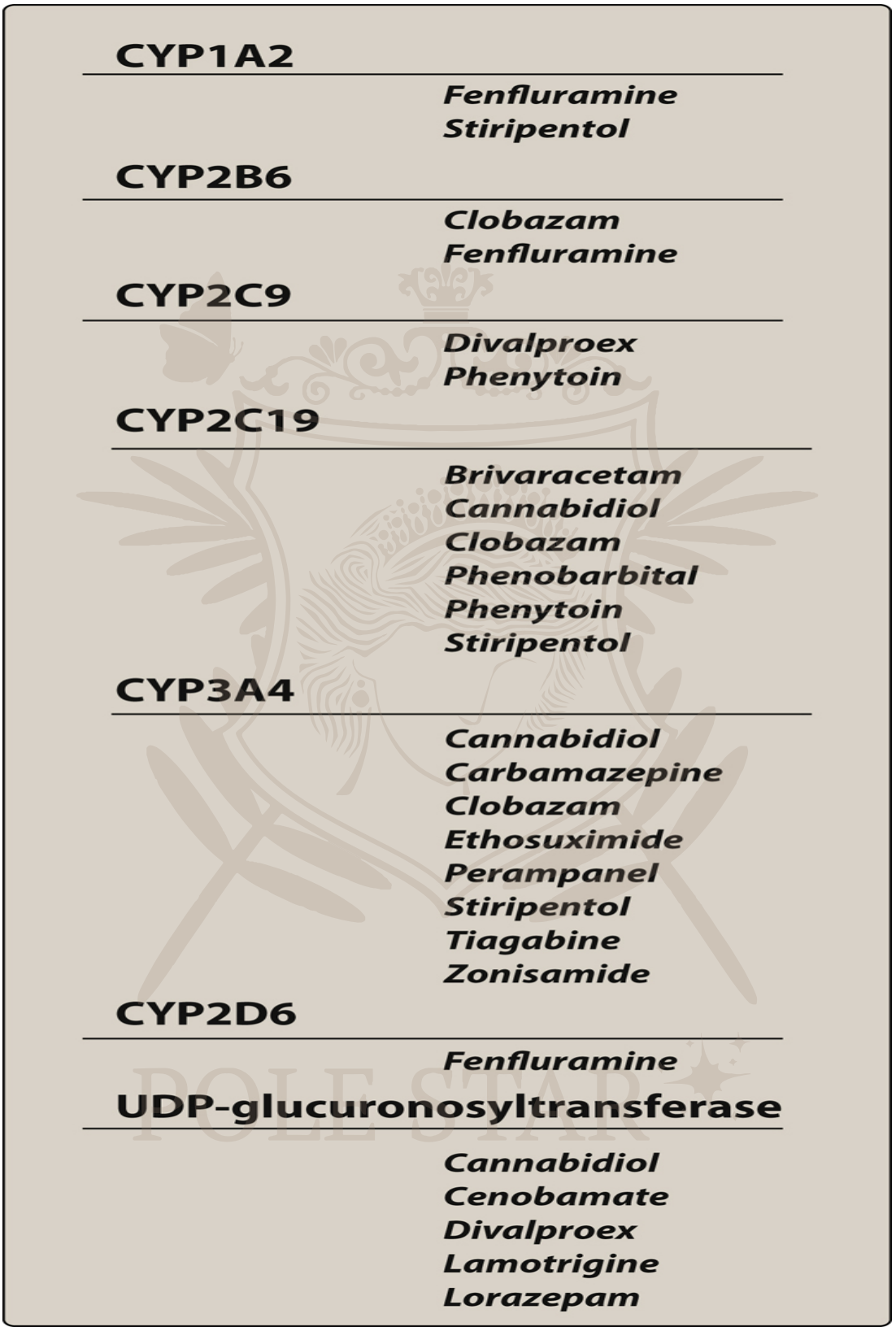

Figure 19.7 CYP metabolism of the antiseizure medications.

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E. Cenobamate

Cenobamate [sen-oh-BAM-ate] is a voltage-gated sodium channel blocker, and it modulates the $GABA_A$ ion channel. It is approved for treating focal seizures. The side effect profile includes fatigue, headache, dizziness, and double vision.

F. Eslicarbazepine

Eslicarbazepine [es-li-kar-BAZ-a-peen] *acetate* is a prodrug that is converted to the active metabolite *eslicarbazepine* (S-licarbazepine) by hydrolysis. S-licarbazepine is the active metabolite of *oxcarbazepine.* It is a voltage-gated sodium channel blocker and is approved for focal seizures. *Eslicarbazepine* exhibits linear pharmacokinetics and is eliminated via glucuronidation. The side-effect profile includes dizziness, somnolence, diplopia, and headache. Serious adverse reactions such as rash, psychiatric side effects, and hyponatremia occur rarely.

G. Ethosuximide

Ethosuximide [eth-oh-SUX-i-mide] reduces propagation of abnormal electrical activity in the brain, most likely by inhibiting T-type calcium channels. It is most effective in treating absence seizures.

H. Felbamate

Felbamate [FEL-ba-mate] has a broad spectrum of anticonvulsant action with multiple proposed mechanisms including the blocking of voltage-dependent sodium channels, competing with the glycine-binding site on the N-methyl-d-aspartate (NMDA) glutamate receptor, blocking of calcium channels, and potentiating GABA action. It is an inhibitor of drugs metabolized by CYP2C19 and induces drugs metabolized by CYP3A4. It is reserved for use in refractory epilepsies (particularly Lennox–Gastaut syndrome) because of the risk of aplastic anemia (about 1:4000) and hepatic failure.

I. Fenfluramine

Fenfluramine [fen-FLUR-uh-meen] is indicated for seizures associated with Dravet syndrome. This agent was originally introduced as a drug

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for obesity but was withdrawn from the market due to concerns of valvular heart disease and pulmonary hypertension. *Fenfluramine* is an agonist at 5-HT_2 receptors, but the mechanism of its anticonvulsant activity in Dravet syndrome is unknown. Adverse effects include drowsiness, lethargy, reduced appetite, and weight loss. Biannual echocardiograms are required to monitor for the development of valvulopathy and pulmonary hypertension.

J. Gabapentin

Gabapentin [GA-ba-pen-tin] is an analog of GABA. However, it does not act at GABA receptors, enhance GABA actions, or convert to GABA. Although gabapentin binds to the $\alpha_2\delta$ subunit of voltage-gated calcium channels, the precise mechanism of action is not known. It is approved as adjunct therapy for focal seizures and treatment of postherpetic neuralgia. *Gabapentin* exhibits nonlinear pharmacokinetics (see Chapter 1) due to its uptake by a saturable transport system from the gut. *Gabapentin* does not bind to plasma proteins and is excreted unchanged through the kidneys. Reduced dosages are required in kidney disease. *Gabapentin* is generally well tolerated due to its relatively mild adverse effects. It may also be a good choice for the older patient because there are few drug interactions.

K. Lacosamide

Lacosamide [la-KOE-sa-mide] affects voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing. *Lacosamide* binds to collapsin response mediator protein-2 (CRMP-2), a phosphoprotein involved in neuronal differentiation and control of axonal outgrowth. The role of CRMP-2 binding in seizure control is unknown. *Lacosamide* is approved for treatment of focal seizures and adjunctive treatment of primary generalized tonic–clonic seizures. The most common adverse events that limit treatment include dizziness, headache, and fatigue.

L. Lamotrigine

Lamotrigine [la-MOE-tri-jeen] blocks sodium channels and high voltage–dependent calcium channels. *Lamotrigine* is effective in a wide variety of seizure types, including focal, generalized, and

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absence seizures, and Lennox–Gastaut syndrome. It is also used to treat bipolar disorder. *Lamotrigine* is metabolized primarily to the 2-N-glucuronide metabolite through the UGT1A4 pathway. As with other antiseizure medications, general inducers increase *lamotrigine* clearance leading to lower *lamotrigine* concentrations, whereas *valproate* results in a significant decrease in *lamotrigine* clearance (higher *lamotrigine* concentrations). *Lamotrigine* dosages should be reduced when adding *valproate* to therapy. Slow titration is necessary with *lamotrigine* (particularly when adding *lamotrigine* to a regimen that includes *valproate*) due to risk of rash, which may progress to a serious, life-threatening reaction.

M. Levetiracetam

Levetiracetam [lee-ve-tye-RA-se-tam] is approved for treatment of focal-onset seizures and adjunct treatment of myoclonic and primary generalized tonic–clonic seizures in adults and children. It demonstrates high affinity for a synaptic vesicle protein (SV2A). The drug is well absorbed after oral administration and is excreted in urine mostly unchanged, resulting in few to no drug interactions. *Levetiracetam* can cause mood alterations that may require a dose reduction or a change of medication.

N. Oxcarbazepine

Oxcarbazepine [ox-kar-BAY-zeh-peen] is a prodrug that is rapidly reduced to the 10-monohydroxy (MHD) metabolite responsible for its anticonvulsant activity. MHD blocks sodium channels and is thought to modulate calcium channels. It is approved for use in adults and children with focal seizures. *Oxcarbazepine* is a less potent inducer of CYP3A4 and UGT than is *carbamazepine.* The adverse effect of hyponatremia limits its use in the elderly.

O. Perampanel

Perampanel [per-AM-pa-nel] is a selective α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid antagonist resulting in reduced excitatory activity. *Perampanel* has a long half-life enabling once-daily dosing. It is approved for treatment of focal seizures and adjunctive treatment of generalized tonic–clonic seizures. This medication has a

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warning for serious psychiatric and behavioral reactions including aggression, hostility, irritability, anger, and homicidal ideation.

P. Phenobarbital and primidone

The primary mechanism of action of *phenobarbital* [fee-noe-BAR-bih-tal] is enhancement of the inhibitory effects of GABA-mediated neurons (see Chapter 16). *Primidone* is metabolized to *phenobarbital* (major) and phenylethylmalonamide, both with anticonvulsant activity. *Phenobarbital* is used primarily in the treatment of status epilepticus when other agents fail.

Q. Phenytoin and fosphenytoin

Phenytoin [FEN-i-toin] blocks voltage-gated sodium channels by selectively binding to the channel in the inactive state and slowing its rate of recovery. It is effective for treatment of focal and generalized tonic–clonic seizures and in the treatment of status epilepticus. *Phenytoin* induces CYP2C and CYP3A families and the UGT enzyme system. *Phenytoin* exhibits saturable enzyme metabolism resulting in nonlinear pharmacokinetic properties (small increases in the daily dose can produce large increases in plasma concentration, resulting in drug-induced toxicity; Figure 19.8). Depression of the CNS occurs particularly in the cerebellum and vestibular system, causing nystagmus and ataxia. The elderly are highly susceptible to this effect. Gingival hyperplasia may cause the gums to grow over the teeth (Figure 19.9). Long-term use may lead to development of peripheral neuropathies and osteoporosis. Although *phenytoin* is advantageous due to its low cost, the actual cost of therapy may be higher, considering the potential for serious toxicity and adverse effects.

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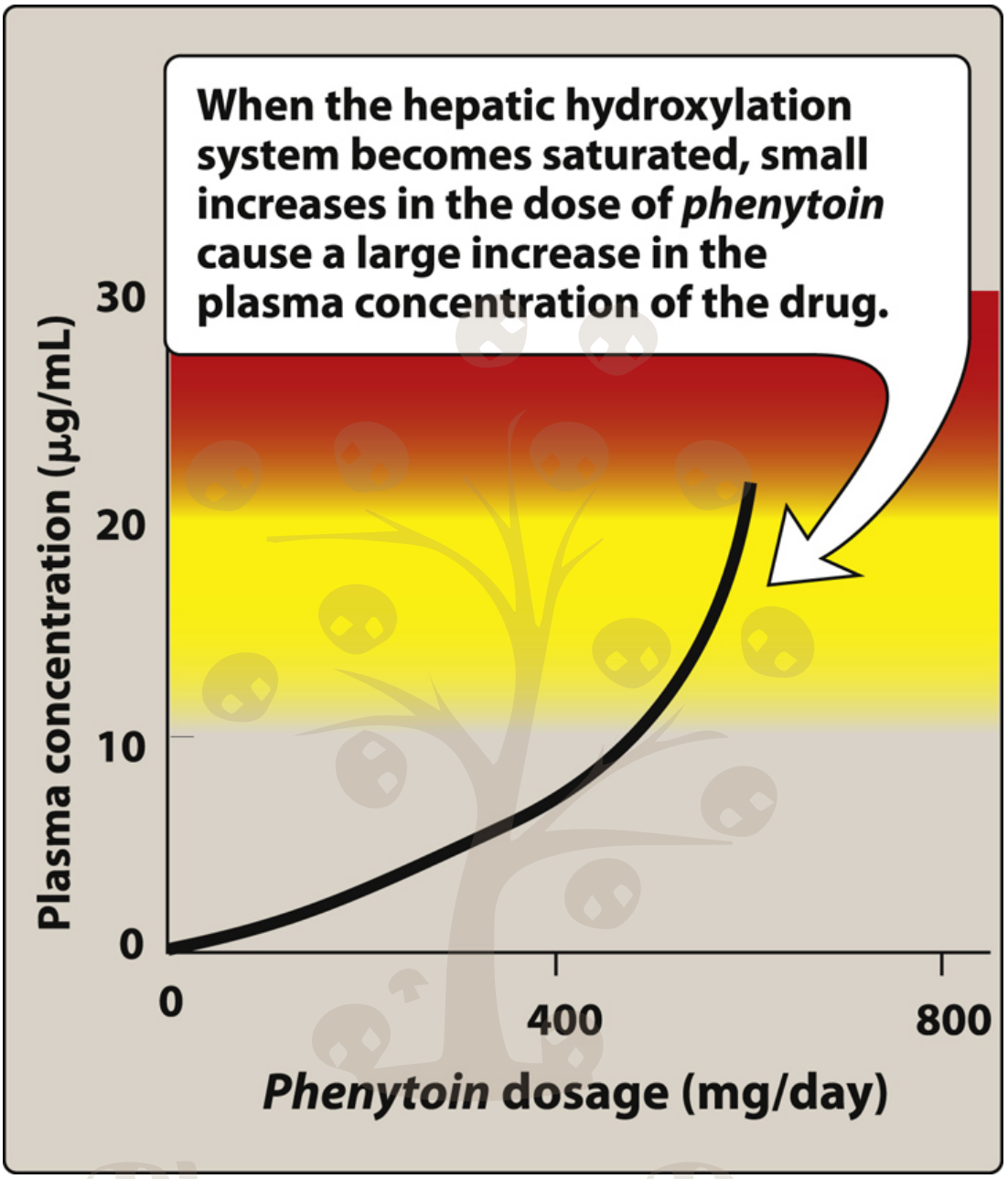

Figure 19.8 Nonlinear effect of phenytoin dosage on the plasma concentration of the drug.

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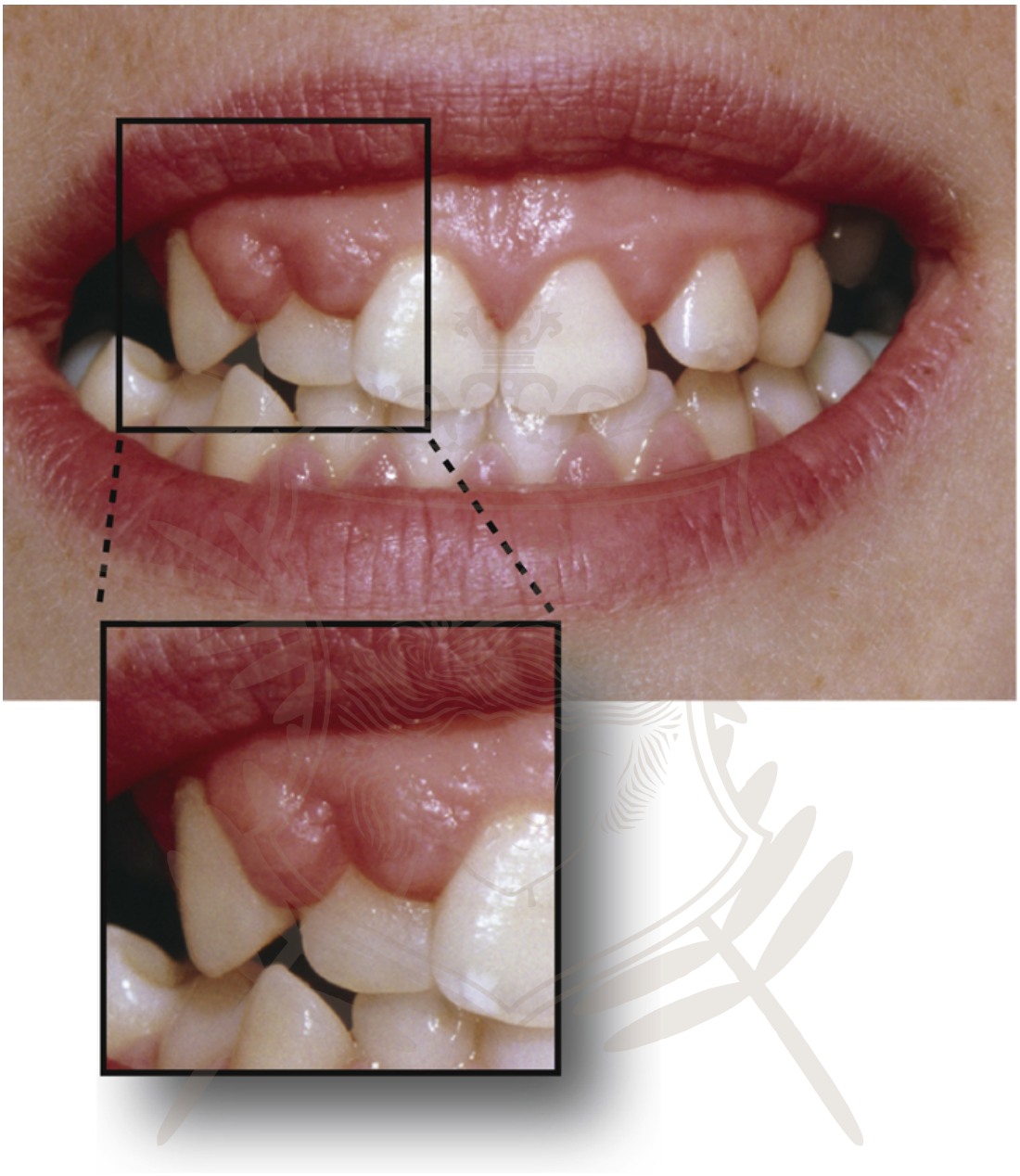

Figure 19.9 Gingival hyperplasia in patient treated with phenytoin.From SCIENCE SOURCE, New York, NY.

Fosphenytoin [FOS-phen-i-toin] is a prodrug that is rapidly converted to *phenytoin* in the blood within minutes. *Fosphenytoin* may be administered intramuscularly (IM), whereas *phenytoin sodium* should never be given IM, as it causes tissue damage and necrosis.

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Fosphenytoin is the drug of choice and standard of care for IV and IM administration of *phenytoin*.

R. Pregabalin

Pregabalin [pree-GA-ba-lin] binds to the $\alpha_2\delta$ site, an auxiliary subunit of voltage-gated calcium channels in the CNS, inhibiting excitatory neurotransmitter release. The drug has proven effects for focal-onset seizures, diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia. More than 90% of *pregabalin* is eliminated renally. It has no significant effects on drug metabolism and few drug interactions. Dosage adjustments are needed in kidney dysfunction.

S. Rufinamide

Rufinamide [roo-FIN-a-mide] acts at sodium channels. It is approved for the adjunctive treatment of seizures associated with Lennox–Gastaut syndrome in children 1 year of age and older and in adults. *Rufinamide* is a weak inhibitor of CYP2E1 and a weak inducer of CYP3A4 enzymes. Food increases absorption and peak serum concentrations. Serum concentrations of *rufinamide* are affected by other antiseizure medications. *Carbamazepine* and *phenytoin* can reduce and *valproate* can increase the serum concentrations of *rufinamide.* Adverse effects include the potential for shortened QT intervals. Patients with familial short QT syndrome should not be treated with *rufinamide*.

T. Stiripentol

Stiripentol [stir-i-PEN-tol] is thought to modulate $GABA_A$ receptors. Its use is limited to patients with Dravet syndrome who are also taking *clobazam.* It is metabolized via CYP1A2, 2C19, and 3A4. When administered with *clobazam*, it significantly increases the concentration of both *clobazam* and the active metabolite (norclobazam).

U. Tiagabine

Tiagabine [tye-AG-a-been] blocks GABA uptake into presynaptic neurons, permitting more GABA to be available for receptor binding and thereby enhancing inhibitory activity. *Tiagabine* is effective as adjunctive treatment in focal seizures. In postmarketing surveillance,

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seizures occurred in patients who did not have epilepsy and were using *tiagabine. Tiagabine* should not be used for indications other than epilepsy.

V. Topiramate

Topiramate [toe-PEER-a-mate] has multiple mechanisms of action. It blocks voltage-dependent sodium channels, reduces high-voltage calcium currents (L type), is a carbonic anhydrase inhibitor, and may act at glutamate (NMDA) sites. *Topiramate* is effective for use in focal and primary generalized epilepsy. It is also approved for prevention of migraine. It mildly inhibits CYP2C19, and coadministration with *phenytoin* and *carbamazepine* may reduce serum concentrations of *topiramate.* Adverse effects include somnolence, weight loss, and paresthesias. Kidney stones, glaucoma, oligohidrosis (decreased sweating), and hyperthermia have also been reported.

W. Valproic acid, valproate, and divalproex

Possible mechanisms of action include sodium channel blockade, blockade of GABA transaminase (GABA-T), and action at the T-type calcium channels. These varied mechanisms provide a broad spectrum of activity against seizures. These agents are effective for the treatment of focal and primary generalized epilepsies. *Valproic acid* [val-PRO-ik A-sid] is available as a free acid. *Divalproex* [dye-val-PRO-ex] *sodium* is a combination of *sodium valproate* [val-PROE-ate] and *valproic acid* that is converted to valproate ion in the gastrointestinal tract. It was developed to improve gastrointestinal tolerance of *valproic acid.* All of the available salt forms are equivalent in efficacy (*valproic acid* and *sodium valproate*). Commercial products are available in multiple-salt dosage forms and extended-release formulations. The large variety in formulations can be confusing, and therefore, the risk for medication errors is high, and it is essential to be familiar with all preparations. *Valproate* inhibits metabolism of the CYP2C9, UGT, and epoxide hydrolase systems (Figure 19.7). Rare hepatotoxicity may cause a rise in liver enzymes, which should be monitored frequently. Use in women and children under age 2 years should be avoided if possible.

X. Vigabatrin

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Vigabatrin [vye-GA-ba-trin] acts as an irreversible inhibitor of GABA-T. GABA-T is the enzyme responsible for metabolism of GABA. *Vigabatrin* is associated with visual field loss ranging from mild to severe in 30% or more of patients. *Vigabatrin* is only available through physicians and pharmacies that participate in the REMS (risk evaluation and mitigation strategies) program.

Y. Zonisamide

Zonisamide [zoe-NIS-a-mide] is a sulfonamide derivative that has a broad spectrum of action. The compound has multiple effects, including blockade of both voltage-gated sodium channels and T-type calcium currents. It has a limited amount of carbonic anhydrase activity. *Zonisamide* is approved for use in patients with focal epilepsy. It is metabolized by the CYP3A4 isozyme and may, to a lesser extent, be metabolized by CYP3A5 and CYP2C19. In addition to typical CNS adverse effects, *zonisamide* may cause kidney stones. Oligohidrosis has been reported, and patients should be monitored for increased body temperature and decreased sweating. *Zonisamide* is contraindicated in patients with sulfonamide or carbonic anhydrase inhibitor hypersensitivity.

VII. STATUS EPILEPTICUS

In status epilepticus, two or more seizures occur without recovery of full consciousness in between episodes. These seizures may be focal or generalized, convulsive or nonconvulsive. Status epilepticus is life threatening and requires emergency treatment usually consisting of parenteral administration of a fast-acting medication such as a benzodiazepine, followed by a slower-acting medication such as *phenytoin*, *fosphenytoin*, *divalproex*, or *levetiracetam*.

VIII. REPRODUCTIVE HEALTH AND EPILEPSY

People of childbearing potential with epilepsy require assessment of their antiseizure medications in regard to contraception and pregnancy

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planning. Several antiseizure medications increase the metabolism of hormonal contraceptives, potentially rendering them ineffective. These include *phenytoin*, *phenobarbital*, *carbamazepine*, *topiramate*, *oxcarbazepine*, *rufinamide*, and *clobazam.* These medications increase the metabolism of contraceptives regardless of the delivery system used (for example, patch, ring, implants, and oral tablets). Pregnancy planning is vital, as many antiseizure medications have the potential to affect fetal development and cause birth defects. All patients considering pregnancy should be on high doses (1-5 mg) of folic acid prior to conception to prevent neural tube defects. *Divalproex* and barbiturates should be avoided in pregnancy when possible. There may be clinical rationale, including treatment failure of other medications, to continue divalproex or barbiturates during pregnancy. If possible, patients already taking *divalproe*x should be placed on other therapies before pregnancy and counseled about the potential for birth defects, including cognitive (Figure 19.10) and behavioral abnormalities and neural tube defects. The pharmacokinetics of antiseizure medications and the frequency and severity of seizures may change during pregnancy. Regular monitoring by both an obstetrician and a neurologist is important. All people of childbearing potential with epilepsy should be encouraged to register with the Antiepileptic Drug Pregnancy Registry. Figure 19.11 summarizes important characteristics of the antiseizure drugs.

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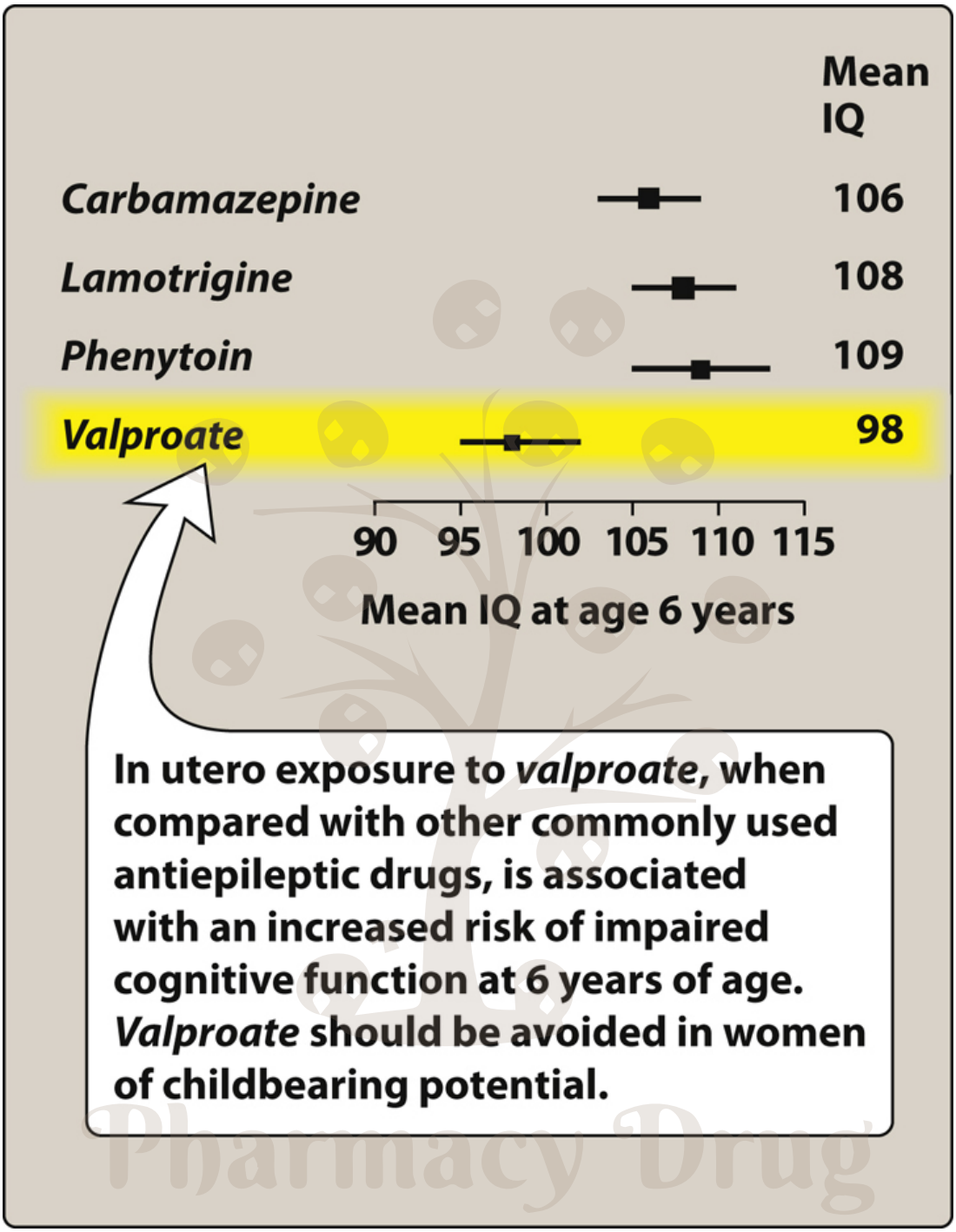

Figure 19.10 Cognitive function at 6 years of age after fetal exposure to doses of antiepileptic drugs.The means (*black squares*) and 95% confidence intervals (*horizontal lines*) are given for the children's IQ as a function of the antiseizure drugs.Data from G. A.Baker , R. L.Bromley , M.Briggs , et al. *Neurology*. 84: 382 (2015).

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DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS AND COMMENTS
Brivaracetam	Binds SV2A	Sedation, dizziness, fatigue, and irritability.
Cannabidiol	Unknown	Somnolence, decreased appetite, diarrhea, elevated liver enzymes, fatigue, poor quality of sleep. Obtain AST, ALT and total bilirubin prior to beginning treatment.
Carbamazepine	Blocks Na^+ channels	Hyponatremia, drowsiness, fatigue, dizziness, and blurred vision. Drug use has also been associated with Stevens-Johnson syndrome. Blood dyscrasias: neutropenia, leukopenia, thrombocytopenia, pancytopenia, and anemias.
Cenobamate	Blocks Na^+ channels and modulates GABA-A channel	Diplopia, dizziness, headache, fatigue. Avoid in patients with familial short QT syndrome.
Divalproex	Multiple mechanisms of action	Weight gain, easy bruising, nausea, tremor, hair loss, GI upset, liver damage, alopecia, and sedation. Hepatic failure, pancreatitis, and teratogenic effects have been observed. Broad spectrum of antiseizure activity.
Eslicarbazepine acetate	Blocks Na^+ channels	Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia.
Ethosuximide	Blocks Ca^{2+} channels	Drowsiness, hyperactivity, nausea, sedation, GI upset, weight gain, lethargy, SLE, and rash. Blood dyscrasias can occur; periodic CBCs should be done. Abrupt discontinuance of drug may cause seizures.
Felbamate	Multiple mechanisms of action	Insomnia, dizziness, headache, ataxia, weight gain, and irritability. Aplastic anemia and hepatic failure. Broad spectrum of antiseizure activity. Requires patient to sign informed consent at dispensing.
Fenfluramine	Unknown	Decreased appetite and weight, somnolence, sedation, lethargy, and diarrhea. Only available via REMS program due to risk of valvular heart disease and pulmonary arterial hypertension.
Gabapentin	Unknown	Mild drowsiness, dizziness, ataxia, weight gain, and diarrhea. Few drug interactions. One hundred percent renal elimination.
Lacosamide	Multiple mechanisms of action	Dizziness, fatigue, and headache. Few drug interactions; Schedule V.
Lamotrigine	Multiple mechanisms of action	Nausea, drowsiness, dizziness, headache, and diplopia. Rash (Stevens-Johnson syndrome—potentially life threatening). Broad spectrum of antiseizure activity.
Levetiracetam	Binds SV2A	Sedation, dizziness, headache, anorexia, fatigue, infections, and behavioral symptoms. Few drug interactions. Broad spectrum of antiseizure activity.
Oxcarbazepine	Blocks Na^+ channels	Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia.
Perampanel	Blocks AMPA glutamate receptors	Serious psychiatric and behavioral reactions, dizziness, somnolence, fatigue, gait disturbance, and falls, long half-life.
Phenytoin	Blocks Na^+ channels	Gingival hyperplasia, confusion, slurred speech, double vision, ataxia, sedation, dizziness, and hirsutism. Stevens-Johnson syndrome—potentially life threatening. Not recommended for chronic use. Primary treatment for status epilepticus (*fosphenytoin*).
Pregabalin	Multiple mechanisms of action	Weight gain, somnolence, dizziness, headache, diplopia, and ataxia. One hundred percent renal elimination; Schedule V.

DRUG	MECHANISM	ADVERSE EFFECTS AND COMMENTS

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DRUG	OF ACTION	ADVERSE EFFECTS AND COMMENTS
Rufinamide	Unknown	Shortened QT interval. Multiple drug interactions.
Stiripentol	GABA-A modulation	Somnolence, decreased appetite, agitation, ataxia, weight loss, hypotonia, nausea, tremor, dysarthria, and insomnia. Neutropenia and thrombocytopenia are also possible.
Tiagabine	Blocks GABA uptake	Sedation, weight gain, fatigue, headache, tremor, dizziness, and anorexia. Multiple drug interactions.
Topiramate	Multiple mechanisms of action	Paresthesia, weight loss, nervousness, depression, anorexia, anxiety, tremor, cognitive complaints, headache, and oligohidrosis. Few drug interactions. Broad spectrum of antiseizure activity.
Vigabatrin	Irreversible binding of GABA-T	Vision loss, anemia, somnolence, fatigue, peripheral neuropathy, weight gain. Available only through SHARE pharmacies.
Zonisamide	Multiple mechanisms of action	Nausea, anorexia, ataxia, confusion, difficulty concentrating, sedation, paresthesia, and oligohidrosis. Broad spectrum of antiseizure activity.

Figure 19.11 Summary of antiseizure drugs.ALT = alanine aminotranferase; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AST = aspartate aminotransferase; CBC = complete blood count; GABA = γ-

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aminobutyric acid; GABA-T = γ-aminobutyric acid transaminase; GI = gastrointestinal; REMS = risk evaluation and mitigation strategies; SLE = systemic lupus erythematosus; SV2A = synaptic vesicle protein.

Clinical Application 19.1 Management of Drug Interactions With Drugs for Epilepsy

As illustrated in Figures 19.5 and 19.7 many agents for epilepsy are metabolized via the liver and have the potential for drug interactions. *Lamotrigine* is used extensively for people of childbearing potential planning for pregnancy due to its lower risk of teratogenicity. *Lamotrigine* is metabolized via UDP-glucuronosyltransferase. *Valproate*, a known inhibitor of *lamotrigine* metabolism, results in significantly decreased clearance of *lamotrigine*, resulting in higher-than-expected *lamotrigine* concentrations than if *lamotrigine* is prescribed as monotherapy. The half-life of *lamotrigine* is also increased from an average of 25 hours to approximately 60 hours in the presence of *valproate. Lamotrigine* also has a high propensity for rash when doses are increased too rapidly. To prescribe *lamotrigine* while a patient is still on *valproate* it should be dosed even more conservatively (starting low dose given every other day) to balance the additional change in metabolism and clearance.

Chapter Summary

- Many drugs are available for the treatment of epilepsy and epilepsy syndromes.
- Agents for epilepsy have varied mechanisms of action, but most drugs reduce seizures through mechanisms such as blocking voltage-gated channels, enhancing inhibitory activities of GABA, or reducing excitatory glutamate transmission.
- When selecting an antiseizure drug, it is critical to know the type of epilepsy or epilepsy syndrome.
- In addition, selection of drugs for epilepsy should be based on:
  - efficacy
  - adverse effects
  - potential for drug interactions
  - comorbidities
  - cost
  - patient preferences
- Drug interactions are common with many antiseizure medications and may be managed with dose adjustments in some cases.
- If a patient is of childbearing potential, the teratogenic risks of the antiseizure drug should be considered. *Divalproex* and barbiturates should be avoided, if possible, in pregnancy.
- Status epilepticus is a medical emergency that requires parenteral treatment with a fast-acting medication such as a benzodiazepine, followed by treatment

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with antiseizure drugs such as *phenytoin*, *fosphenytoin*, *divalproex*, or *levetiracetam.*

STUDY QUESTIONS

Choose the ONE best answer.

19.1 A 9-year-old boy is sent for neurologic evaluation because of episodes of apparent inattention. Over the past year, the child has experienced episodes during which he develops a blank look on his face and his eyes blink for 15 seconds. He immediately resumes his previous activity. Which of the following best describes seizures in this patient?

A. Focal
B. Tonic–clonic
C. Absence
D. Myoclonic

Correct answer = C. The patient is experiencing episodes of absence seizures where consciousness is impaired briefly. Absence seizures generally begin in children aged 4 to 12 years. Diagnosis includes obtaining an electroencephalogram that shows generalized 3-Hz waves.

19.2 A child is experiencing absence seizures that interrupt his ability to pay attention during school and activities. Which therapy is most appropriate for this patient?

A. Ethosuximide
B. Carbamazepine
C. Diazepam
D. Watchful waiting

Correct answer = A. The patient has had many seizures that interrupt his ability to pay attention during school and activities, so therapy is justified. Carbamazepine may make the seizures more frequent. Diazepam is not indicated for absence seizures.

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19.3 A 25-year-old woman with generalized seizures is well controlled on valproate. She indicates that she is interested in becoming pregnant in the next year. With respect to her antiseizure medication, which of the following should be considered?

A. Leave her on her current therapy.
B. Consider switching to lamotrigine.
C. Consider adding a second antiseizure medication.
D. Decrease her valproate dose.

Correct answer = B. Valproate is a poor choice in women of childbearing age and should be avoided if possible. A review of the medication history of this patient is warranted. If she has not tried any other antiseizure medication, then consideration of another antiseizure medication may be beneficial. Studies show that valproate taken during pregnancy can have a detrimental effect on cognitive abilities in children. However, treatment with valproate may not be avoidable as it could be the only choice for some women. In these cases, the lowest effective dose should be used.

19.4 A 52-year-old man has had several focal seizures with impaired consciousness over the last year. Which of the following is the most appropriate initial therapy for this patient?

A. Ethosuximide
B. Levetiracetam
C. Diazepam
D. Carbamazepine plus primidone

Correct answer = B. The patient has had many seizures, and the risks of not starting drug therapy would be substantially greater than the risks of treating his seizures. Because the patient has impaired consciousness during the seizure, he is at risk for injury during an attack. Monotherapy with primary agents is preferred for most patients. The advantages of monotherapy include reduced frequency of adverse effects, absence of interactions between antiepileptic drugs, lower cost, and improved compliance. Ethosuximide and diazepam are not indicated for focal seizures.

19.5 A patient with focal seizures has been treated for 6 months with carbamazepine, but recently has been experiencing breakthrough seizures on a more frequent basis. Addition of a second drug to the antiseizure regimen is being considered. Which of the following

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drugs is least likely to have a pharmacokinetic interaction with the patient's current regimen?

A. Topiramate
B. Tiagabine
C. Levetiracetam
D. Lamotrigine

Correct answer = C. Of the drugs listed, all of which are approved as adjunct therapy for refractory focal seizures, only levetiracetam does not affect the pharmacokinetics of other antiepileptic drugs, and other drugs do not significantly alter its pharmacokinetics. However, any of the listed drugs could be added depending on the plan and the patient characteristics. Treatment of epilepsy is complex, and diagnosis is based on history and may need to be reevaluated when drug therapy fails or seizures increase.

19.6 A 75-year-old woman had a stroke approximately 1 month ago. She is continuing to have small focal seizures where she fails to respond appropriately to questions. Which of the following is the most appropriate treatment for this individual?

A. Phenytoin
B. Oxcarbazepine
C. Gabapentin
D. Phenobarbital

Correct answer = C. Gabapentin is well tolerated in the elderly due to its mild side-effect profile, and it has few drug interactions. Since elderly patients may have reduced kidney function, the dosage should be decreased appropriately. Oxcarbazepine may cause hyponatremia, which is more symptomatic in the elderly. Phenytoin and phenobarbital have many drug interactions and a side effect profile that may be especially troublesome in the elderly age group, including dizziness that may lead to falls, cognitive issues, and bone health issues.

19.7 A 17-year-old patient with a diagnosis of Dravet syndrome is being considered for a trial of cannabidiol. What baseline lab should be checked before beginning cannabidiol?

A. Serum creatinine
B. Total protein

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C. Total cholesterol
D. Alanine aminotransferase

Correct answer = D. Baseline liver function tests, such as alanine aminotransferase, aspartate aminotransferase, and bilirubin should be checked prior to starting cannabidiol, as cannabidiol treatment may elevate liver function tests. Serum creatinine is not needed because the primary elimination of cannabidiol is via the liver. Protein and cholesterol are not parameters related to medication safety for cannabidiol.

19.8 A 62-year-old patient has new-onset seizures after a head trauma. The patient has a history of hypertension, which is managed with hydrochlorothiazide (decreases sodium level in blood). Addition of which of the following antiseizure drugs may increase the risk of hyponatremia in this patient?

A. Gabapentin
B. Divalproex
C. Carbamazepine
D. Lacosamide

Correct answer = C. Carbamazepine is associated with hyponatremia. When used in combination with other medications that decrease sodium, it increases the chance of hyponatremia. Gabapentin, divalproex, and lacosamide are not known to alter sodium concentrations.

19.9 A 34-year-old obese patient with focal seizures that progress to generalized tonic–clonic seizures is currently taking lamotrigine and levetiracetam. She is continuing to have a seizure every 4 months. She is not currently planning to have children and is taking oral contraceptives. Which of the following antiseizure drugs is most appropriate to add?

A. Brivaracetam
B. Lacosamide
C. Zonisamide
D. Carbamazepine

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Correct answer = C. Zonisamide has a broad spectrum of action, does not interact with oral contraceptives, and can result in weight loss. Brivaracetam is similar in mechanism of action to levetiracetam, so addition would not be appropriate. Lacosamide works by blocking sodium channels, which is also a primary mechanism of action of lamotrigine. Carbamazepine decreases the efficacy of oral contraceptives due to enzyme induction and also works primarily through blocking of sodium channels.

19.140 14-year-old boy with generalized tonic–clonic seizures is experiencing occasional breakthrough seizures. He lives 1 hour away from the nearest hospital. Which of the following treatments is most appropriate to suggest to his family for as-needed treatment of breakthrough seizures at home?

A. Topical hemp lotion (contains cannabidiol)
B. Intranasal diazepam
C. Oral clonazepam
D. Oral lamotrigine

Correct answer = B. Intranasal or rectal diazepam can be used to treat clusters of seizures at home, which may help a patient avoid hospitalization. Hemp lotion is not subject to oversight and regulations that approved drug products are held to and would most likely contain a small, nontherapeutic amount of cannabidiol. Clonazepam is a possible as-needed medication; however, administration of an oral product would not be practical.

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20

Anesthetics

Brandon M. Lopez, Chris R. Giordano

I. OVERVIEW

For patients undergoing surgical or medical procedures, different levels of sedation can provide important benefits to facilitate procedural interventions. These levels of sedation range from anxiolysis to general anesthesia and can create:

- Sedation and reduced anxiety
- Lack of awareness and amnesia
- Skeletal muscle relaxation
- Suppression of undesirable reflexes
- Analgesia

Because no single agent provides all desired objectives, several categories of drugs are combined to produce the optimum level of sedation required (Figure 20.1). Drugs are chosen to provide safe and efficient sedation based on the type and duration of the procedure and patient characteristics, such as organ function, medical conditions, and concurrent medications (Figure 20.2). Preoperative drugs provide anxiolysis and analgesia and mitigate unwanted side effects of the anesthetic or the procedure itself. Neuromuscular blockers enable endotracheal intubation and muscle relaxation to facilitate surgery. Potent general anesthetic drugs are delivered via inhalation and/or intravenously. Except for *nitrous oxide*, inhaled anesthetics are volatile, halogenated hydrocarbons, while intravenous (IV) anesthetics consist of several chemically

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unrelated drug classes commonly used to rapidly induce and/or maintain a state of general anesthesia.

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PREOPERATIVE MEDICATIONS

Analgesics
Antacids
Antiemetics
Benzodiazepines*

ANALGESICS

Acetaminophen TYLENOL, OFIRMEV
Celecoxib CELEBREX
Gabapentin NEURONTIN
Ketamine KETALAR*
Opioids (see Chapter 21)

GENERAL ANESTHETICS: INHALED

Desflurane SUPRANE
Isoflurane FORANE
Nitrous oxide GENERIC ONLY
Sevoflurane ULTANE

GENERAL ANESTHETICS: INTRAVENOUS

Dexmedetomidine PRECEDEX
Etomidate AMIDATE
Methohexital BREVITAL
Propofol DIPRIVAN

NEUROMUSCULAR BLOCKERS (see Chapter 5)

Cisatracurium, mivacurium, pancuronium, rocuronium, succinylcholine, vecuronium

LOCAL ANESTHETICS: AMIDES

Bupivacaine MARCAINE
Lidocaine XYLOCAINE
Mepivacaine CARBOCAINE
Ropivacaine NAROPIN

LOCAL ANESTHETICS: ESTERS

Chloroprocaine NESACAINE
Tetracaine GENERIC ONLY

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Figure 20.1 Summary of common drugs used for anesthesia.*Can cause general anesthesia with higher doses. See Chapter 5 for summary of neuromuscular blocking agents.

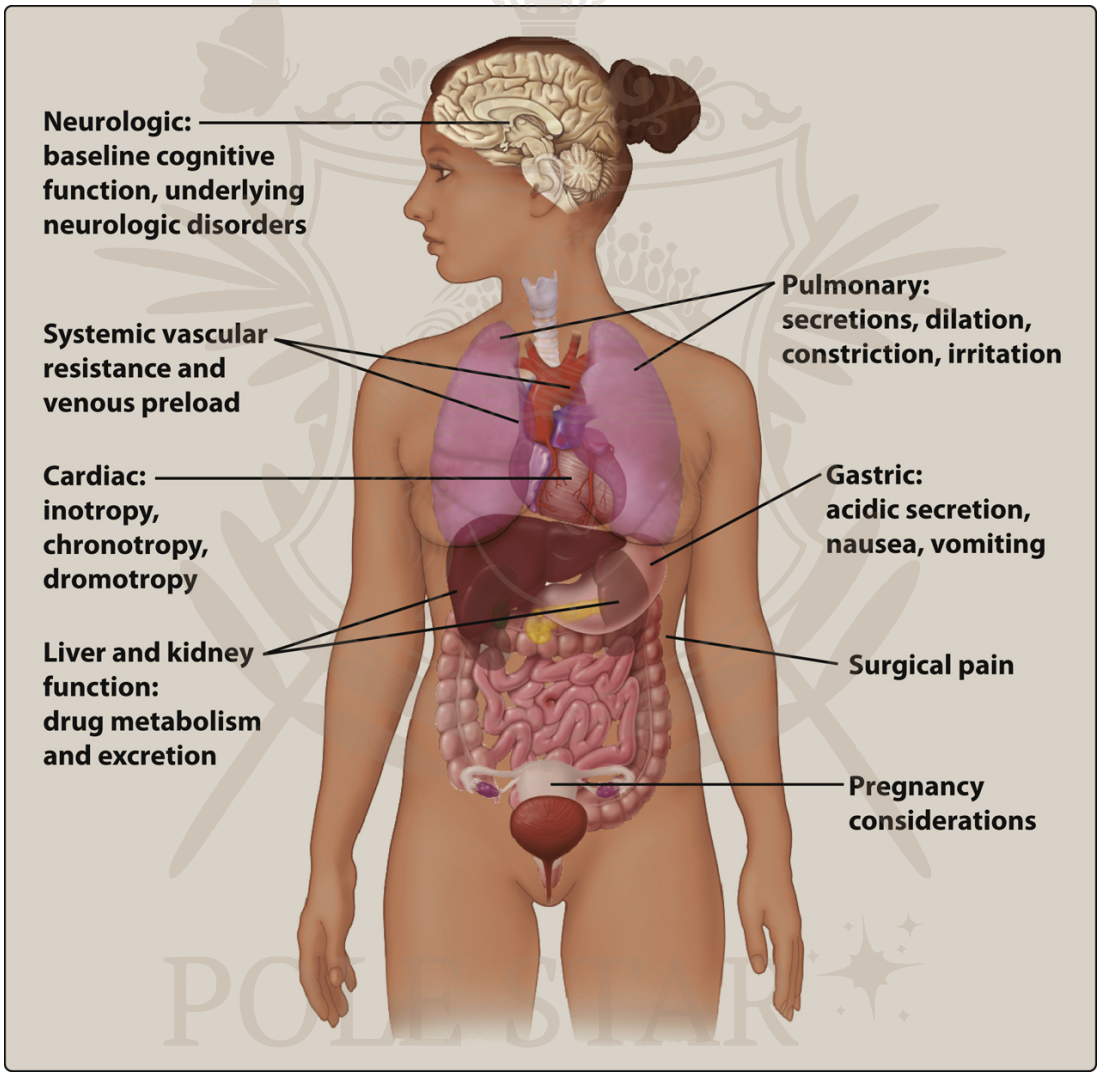

Figure 20.2 Overall considerations when delivering an anesthetic.

II. LEVELS OF SEDATION

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The levels of sedation occur in a dose-related continuum, which is variable and depends on individual patient response to various drugs. These "artificial" levels of sedation start with light sedation (anxiolysis) and continue to moderate sedation, then deep sedation, and finally a state of general anesthesia. The hallmarks of escalation from one level to the next are recognized by changes in mentation, hemodynamic stability, and respiratory competency (Figure 20.3). This escalation in levels is often very subtle and unpredictable; therefore, the sedation provider must always be ready to manage the unanticipated next level of sedation.

	MINIMAL (ANXIOLYSIS)	MODERATE	DEEP	GENERAL
Mentation	Responds normally to verbal stimuli	Responds purposefully to verbal or tactile stimuli	Responds purposefully to repeated verbal or painful stimuli	Unarousable to painful stimuli
Airway competency	Unaffected	Adequate	Intervention may be required	Intervention usually required
Respiratory system	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular system	Unaffected	Usually maintained	Usually maintained	May be impaired

Figure 20.3 Anesthetic levels of sedation.

III. STAGES OF GENERAL ANESTHESIA

General anesthesia is a reversible state of central nervous system (CNS) depression, causing loss of response to and perception of stimuli. The state of general anesthesia can be divided into three stages: induction, maintenance, and emergence. Induction is the time from administration of a potent anesthetic to development of unconsciousness, while maintenance is the sustained period of general anesthesia. Emergence (also known as recovery) starts with the discontinuation of the anesthetic and continues until the return of consciousness and protective reflexes. Induction of anesthesia depends on how fast effective concentrations of anesthetic reach the

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brain. Emergence is essentially the reverse of induction and depends on how fast the anesthetic diffuses from the brain. The depth of general anesthesia is the degree to which the CNS is depressed, as evident in electroencephalograms.

A. Induction

General anesthesia in adults is normally induced with an IV agent like *propofol*, producing unconsciousness in 30 to 40 seconds. Often, an IV neuromuscular blocker such as *rocuronium*, *vecuronium*, or *succinylcholine* is administered to facilitate endotracheal intubation by eliciting muscle relaxation. For children without IV access, nonpungent volatile agents, such as *sevoflurane*, are administered via inhalation to induce general anesthesia.

B. Maintenance of anesthesia

After administering the induction drug, vital signs and response to stimuli are vigilantly monitored to balance the amount of drug continuously inhaled or infused to maintain general anesthesia. Maintenance is commonly provided with volatile anesthetics, although total intravenous anesthesia (TIVA) with drugs like *propofol* can be used to maintain general anesthesia. Opioids such as *fentanyl* are used for analgesia along with inhalation agents, because the latter alter consciousness but not perception of pain.

C. Emergence

After cessation of the maintenance anesthetic drug, the patient is evaluated for return of consciousness. For most anesthetic agents, redistribution from the site of action (rather than metabolism of the drug) underlies recovery. Neuromuscular blocking drugs are typically reversed after completion of surgery, unless enough time has elapsed for their metabolism. The patient is monitored to assure full recovery of all normal physiologic functions (spontaneous respiration, blood pressure, heart rate, and all protective reflexes).

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IV. INHALATION ANESTHETICS

Inhaled gases are used primarily for maintenance of anesthesia after administration of an IV drug (Figure 20.4). Depth of anesthesia can be rapidly altered by changing the inhaled gas concentration. Inhalational agents have steep dose–response curves with very narrow therapeutic indices, so the difference in concentrations from eliciting general anesthesia to cardiopulmonary collapse is small. No antagonists exist. To minimize waste, inhaled gases are delivered in a recirculation system that contains absorbents to remove carbon dioxide and allow rebreathing of the gas. Recently, there has been greater attention to the anthropogenic emissions of these potent greenhouse gases, which are typically released from hospital rooftops after each procedure.

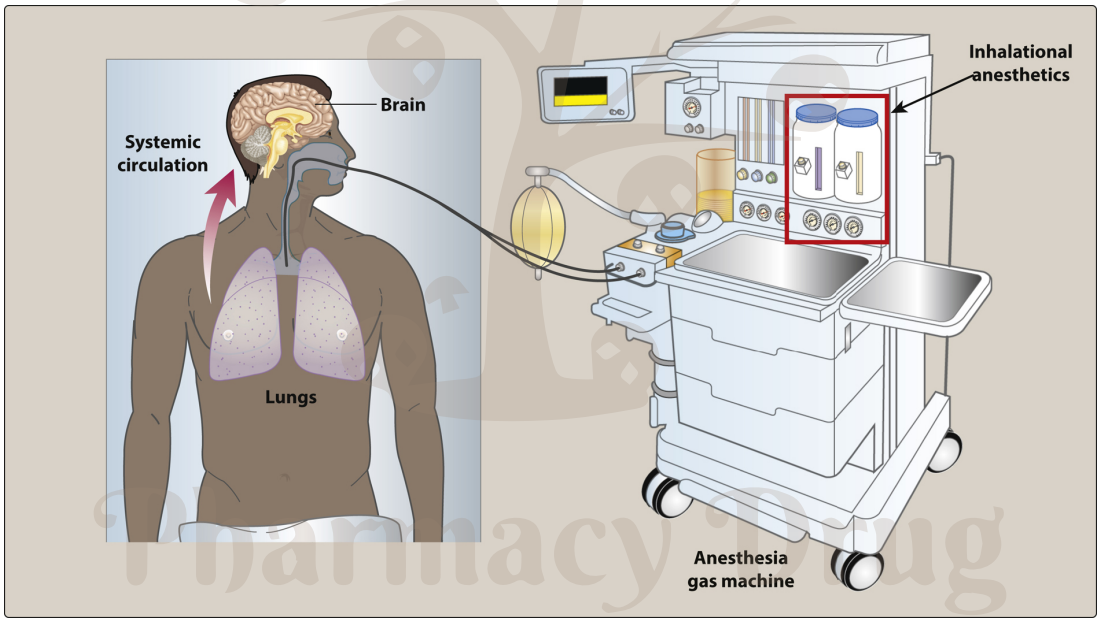

Figure 20.4 Volatile anesthetics delivered to the patient are absorbed via the lungs into the systemic circulation causing dose-dependent CNS depression.

A. Common features of inhalation anesthetics

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Modern inhalation anesthetics are nonflammable, nonexplosive agents, which include *nitrous oxide* and volatile, halogenated hydrocarbons (*isoflurane*, *sevoflurane*, and *desflurane*). These agents decrease cerebrovascular resistance, resulting in increased brain perfusion. They cause bronchodilation and also decrease both respiratory drive and hypoxic pulmonary vasoconstriction (increased pulmonary vascular resistance in poorly oxygenated regions of the lungs, redirecting blood flow to better oxygenated regions). Movement of these gases from the lungs to various body compartments depends upon their solubility in blood and tissues, as well as on blood flow. The following factors play a role in induction and emergence:

B. Potency

Potency is defined quantitatively as the minimum alveolar concentration (MAC), which is the end-tidal concentration of inhaled anesthetic needed to eliminate movement in 50% of patients exposed to a noxious stimulus. MAC is the median effective dose (ED_{50}) of the anesthetic, expressed as the percentage of gas in a mixture required to achieve that effect. Numerically, MAC is small for potent anesthetics such as *isoflurane* and large for less potent agents such as *nitrous oxide.* Thus, the inverse of MAC is an index of potency (Figure 20.5). *Nitrous oxide* alone cannot produce general anesthesia because any admixture with a survivable oxygen percentage cannot reach its MAC value. The more lipid soluble an anesthetic, the lower the concentration needed to produce anesthesia and, therefore, the higher the potency. Factors that can increase MAC (make the patient more resistant) include hyperthermia, drugs that increase CNS catecholamines, and chronic ethanol abuse. Factors that can decrease MAC (make the patient more sensitive) include increased age, hypothermia, pregnancy, sepsis, acute intoxication, concurrent IV anesthetics, and α_2-adrenergic receptor agonists (*clonidine* and *dexmedetomidine*).

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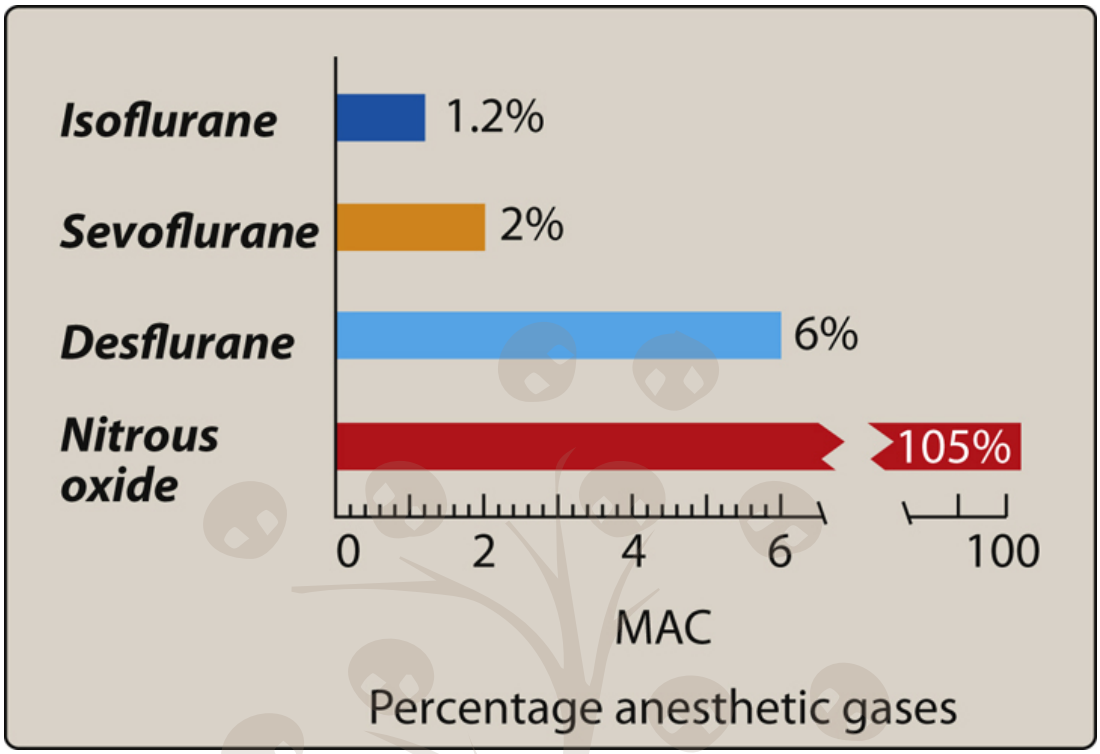

Figure 20.5 Minimal alveolar concentrations (MAC) for anesthetic gases are used to compare pharmacologic effects of different agents (high MAC = low potency).

C. Uptake and distribution of inhalation anesthetics

The principal objective of inhalation anesthesia is a constant and optimal brain partial pressure (P_{br}) of inhaled anesthetic (to create a partial pressure equilibrium between alveoli [P_{alv}] and brain [P_{br}]). Measuring the P_{alv} is the most practical and feasible way to ascertain the P_{br} for the inhaled anesthetic concentration, but this necessitates adequate time for the two compartments to reach equilibrium. The partial pressure of an anesthetic gas that originates by pulmonary entry is the driving force moving the gas from the alveolar space into the bloodstream (P_a), which transports the drug to the brain and other body compartments. Because gases move from one body compartment to another according to partial pressure gradients, steady state is achieved

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when the partial pressure in each of these compartments is equivalent to that in the inspired mixture. [Note: At equilibrium, $P_{alv} = P_a = P_{br}$.] The time course for attaining this steady state is determined by the following factors:

1. **Alveolar wash-in:** This refers to replacement of normal lung gases with the inspired anesthetic mixture. The time required for this process is directly proportional to the functional residual capacity of the lung (volume of gas remaining in the lungs at the end of a normal expiration) and inversely proportional to ventilatory rate. It is independent of the physical properties of the gas. As the partial pressure builds within the lung, anesthetic gas transfer from the lung begins.

2. **Anesthetic uptake (removal to peripheral tissues other than the brain):** Uptake is the product of the gas solubility in the blood, cardiac output (CO), and gradient between alveolar and blood anesthetic partial pressures.

    a. **Solubility in blood:** This is determined by a physical property of the anesthetic called the blood:gas partition coefficient (the ratio of the concentration of anesthetic in the liquid [blood] phase to the concentration of anesthetic in the gas phase when the anesthetic is in equilibrium between the two phases; Figure 20.6). For inhaled anesthetics, think of the blood as a pharmacologically inactive reservoir. Drugs with low versus high blood solubility differ in their rate of induction of anesthesia. When an anesthetic gas with low blood solubility such as *nitrous oxide* diffuses from the alveoli into the circulation, little anesthetic dissolves in the blood. Therefore, equilibrium between the inspired anesthetic and arterial blood occurs rapidly with relatively few additional molecules of anesthetic required to raise the arterial anesthetic partial pressure. By contrast, anesthetic gases with high blood solubility, such as *isoflurane*, dissolve more

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fully in the blood; therefore, greater amounts of gas and longer periods of time are required to raise blood partial pressure. This results in longer periods for induction, recovery, and time to change in depth of anesthesia in response to changes in the drug concentration. The solubility in blood is ranked as follows: *isoflurane* > *sevoflurane* > *nitrous oxide* > *desflurane*.

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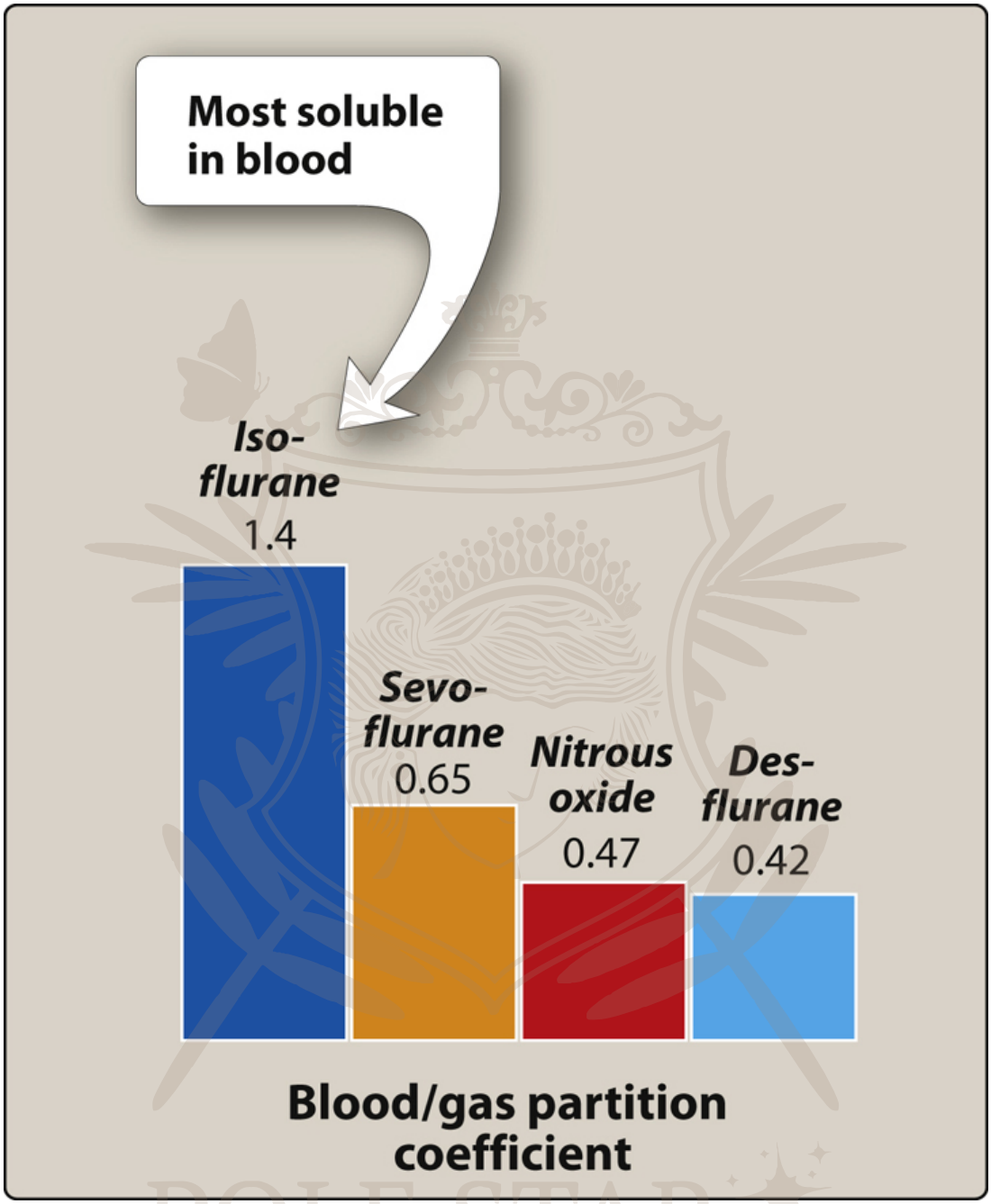

Figure 20.6 Blood/gas partition coefficients for some inhalation anesthetics.

b. Cardiac output: CO is inversely correlated with induction time for inhaled anesthetics. This counterintuitive phenomenon is explained by the threshold of drug

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concentration required to alter neuronal activity and the time neurons are exposed to the drug in the passing blood. During low CO, a longer period of time permits a larger concentration of gas to dissolve in the slowly moving bloodstream. Furthermore, this large bolus of drug has longer contact time to diffuse into neuronal tissue when it traverses the blood–brain barrier. Although a high CO will quickly transport the drug to the brain, a lower concentration of the drug with a shorter exposure time slows down the rate of induction.

c. Alveolar-to-venous partial pressure gradient: This gradient between the alveolar and returning venous gas partial pressure results from the tissue uptake from the arterial delivery. The arterial circulation distributes the anesthetic to various tissues, and tissue uptake is dependent on the tissue blood flow, blood-to-tissue partial pressure difference, and blood-to-tissue solubility coefficient. As venous circulation returns to the lung blood with low or no dissolved anesthetic gas, this high gradient causes gas to move from the alveoli into the blood. If a large alveolar-to-venous partial pressure gradient persists, the peripheral tissue gas uptake must be high, and therefore, the induction time is longer. Over time, as the partial pressure of gas in venous blood approximates the inspired mixture and subsequent alveolar concentration, no further uptake from the lung occurs.

3.Effect of different tissue types on anesthetic uptake: The time required for a tissue compartment to reach steady state with the partial pressure of the inspired anesthetic gas is inversely proportional to the blood flow to that tissue (greater flow equals less time to reach equilibrium). Time to steady state is directly proportional to the capacity of that tissue to store anesthetic (greater storage capacity equals longer time to reach equilibrium). Furthermore, capacity is

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directly proportional to the volume of tissue and the tissue:blood solubility coefficient of the gas. Four major tissue compartments determine the time course of anesthetic uptake:

a. **Vessel-rich group (brain, heart, liver, kidney, and endocrine glands):** Highly perfused tissues rapidly attain steady state with the partial pressure of anesthetic in the blood.

b. **Skeletal muscles:** These tissues are moderately perfused with a large storage capacity, which lengthens the time required to achieve steady state.

c. **Fat:** Fat is poorly perfused but has a very large storage capacity for the highly lipophilic volatile anesthetics. This poor perfusion to a high-capacity compartment drastically prolongs the time required to achieve steady state.

d. **Vessel-poor group (bone, ligaments, and cartilage):** These are very poorly perfused and have a low capacity to store anesthetic gas. Therefore, these tissues have minimal impact on the time course of anesthetic distribution in the body.

4.Washout: When an inhalation anesthetic gas is removed from the inspired admixture, the body becomes the repository of anesthetic gas to be circulated back to the alveolar compartment. The same factors that influence uptake and equilibrium of the inspired anesthetic determine the time course of its exhalation from the body. Thus, *nitrous oxide* exits the body faster than does *isoflurane* (Figure 20.7).

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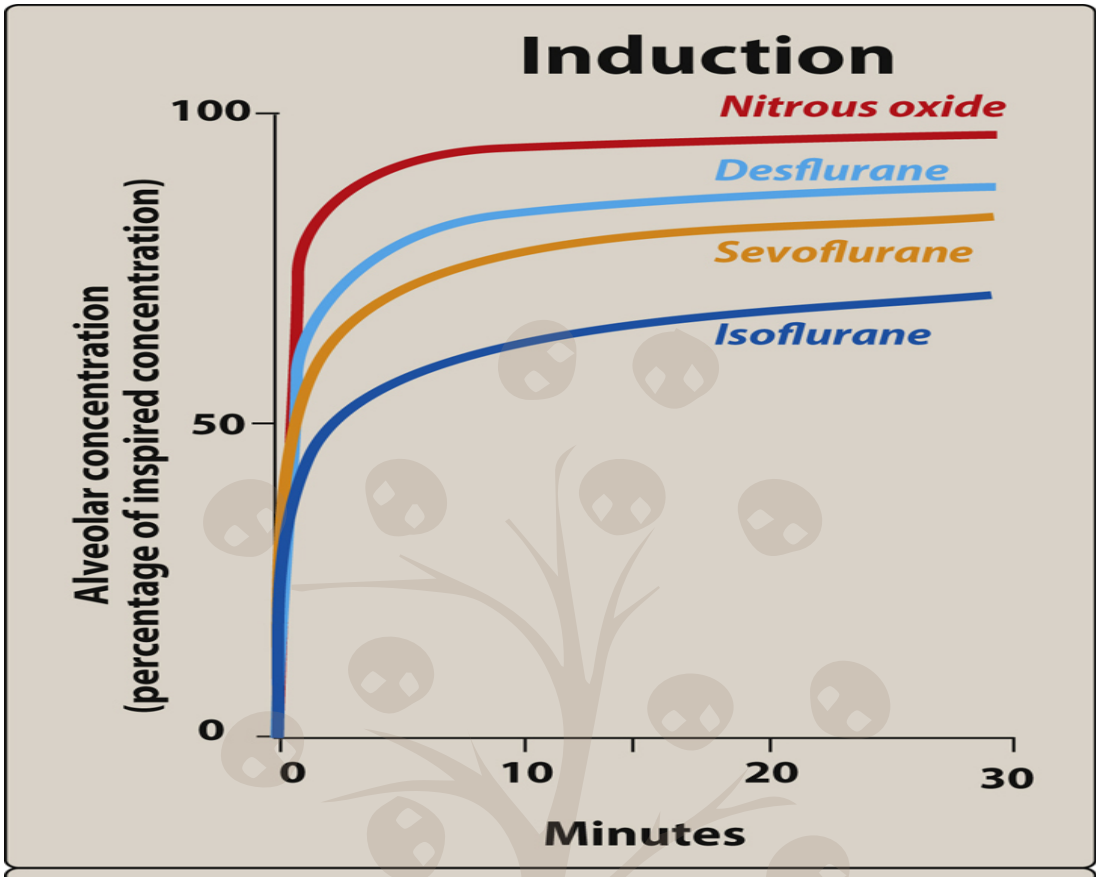

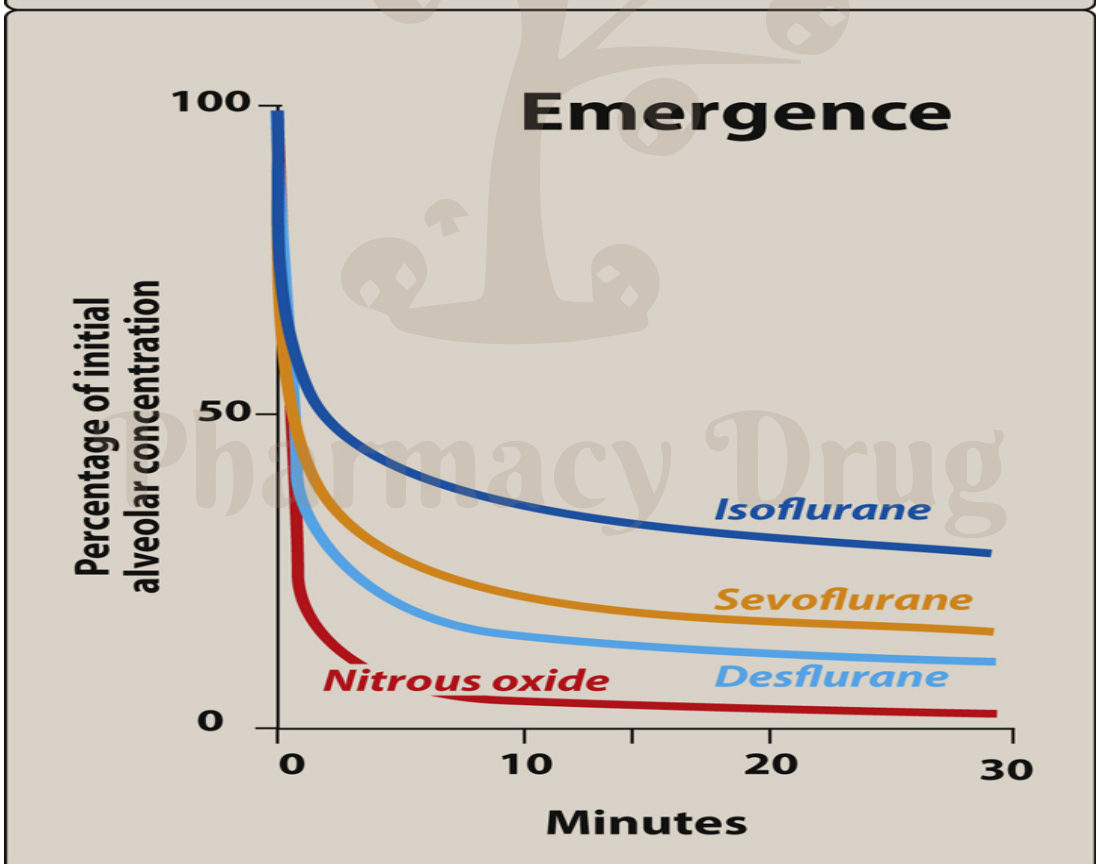

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Figure 20.7 Changes in the alveolar blood concentrations of some inhalation anesthetics over time.

D. Mechanism of action

No specific receptor has been identified as the locus to create a state of general anesthesia. The fact that chemically unrelated compounds produce unconsciousness argues against the existence of a single receptor, and it appears that a variety of molecular mechanisms may contribute to the activity of anesthetics. At clinically effective concentrations, general anesthetics increase the sensitivity of the γ-aminobutyric acid ($GABA_A$) receptors to the inhibitory neurotransmitter GABA. This increases chloride ion influx and hyperpolarization of neurons. Postsynaptic neuronal excitability and, thus, CNS activity are diminished (Figure 20.8). Unlike other anesthetics, *nitrous oxide* and *ketamine* do not have actions on $GABA_A$ receptors. Their effects are mediated via inhibition of *N*-methyl-d-aspartate (NMDA) receptors. [Note: The NMDA receptor is a glutamate receptor, which is the body's main excitatory neurotransmitter.] Receptors other than GABA that are affected by volatile anesthetics include the inhibitory glycine receptors found in the spinal motor neurons. Additionally, inhalation anesthetics block excitatory postsynaptic currents found on nicotinic receptors. However, the mechanisms by which anesthetics perform these modulatory roles are not fully understood.

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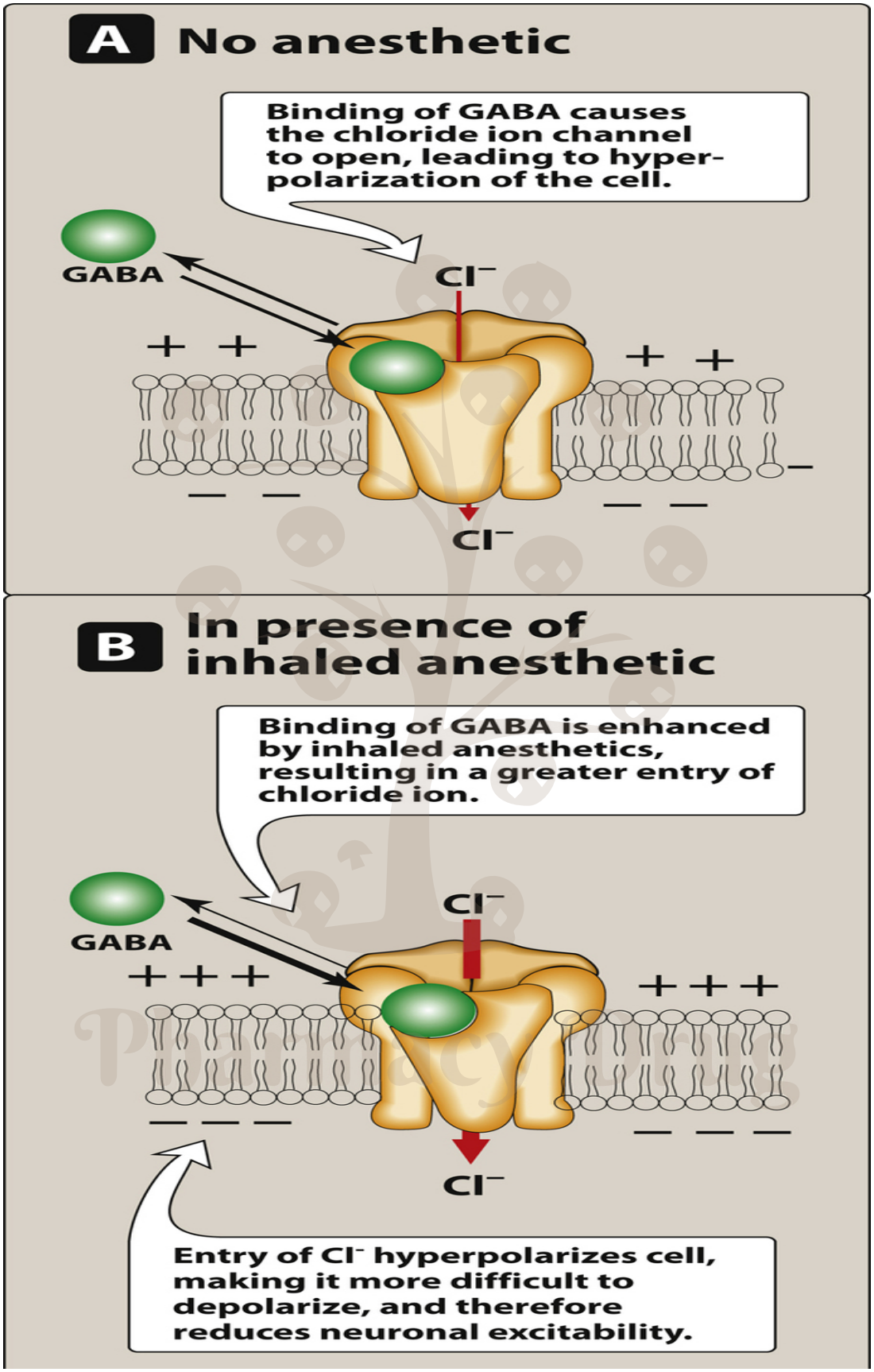

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Figure 20.8 An example of modulation of a ligand-gated membrane channel modulated by inhaled anesthetics.Cl^- = chloride ion; GABA = γ-aminobutyric acid.

E. Isoflurane

Isoflurane [eye-so-FLOOR-ane] has become the prototypical halogenated hydrocarbon since *halothane* was discontinued. Like other halogenated gases, *isoflurane* produces dose-dependent hypotension predominantly from relaxation of systemic vasculature. Hypotension can be treated with a direct-acting vasoconstrictor, such as *phenylephrine* (see Chapter 6). Because it undergoes little metabolism, *isoflurane* is considered nontoxic to the liver and kidney. Its pungent odor stimulates respiratory reflexes (breath holding, salivation, coughing, laryngospasm), so it is not used for inhalation induction. With a higher blood solubility than *desflurane* and *sevoflurane*, *isoflurane* takes longer to reach equilibrium, making it less ideal for short procedures; however, its low cost makes it a good option for longer surgeries.

F. Desflurane

Desflurane [DES-floor-ane] provides very rapid onset and emergence due to low blood solubility. This makes it a popular anesthetic for short procedures. It has a low volatility, which requires administration via a special heated vaporizer. Like *isoflurane*, it decreases vascular resistance and perfuses all major tissues very well. *Desflurane* has significant respiratory irritation like *isoflurane* so it should not be used for inhalation induction. Its degradation is minimal and tissue toxicity is rare. Higher cost occasionally prohibits its use.

G. Sevoflurane

Sevoflurane [see-voe-FLOOR-ane] has low pungency or respiratory irritation. This makes it useful for inhalation induction,

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especially with pediatric patients who do not tolerate IV placement. It has a rapid onset and recovery due to low blood solubility. *Sevoflurane* has low hepatotoxic potential, but compounds formed (compound A) from reactions in the anesthesia circuit (soda lime) may be nephrotoxic with very low fresh gas flow that allows longer chemical reaction time. It is recommended when using soda lime absorbents in the anesthesia circuit to keep fresh gas flows above 2 liters per minute to prevent the formation of this nephrotoxic chemical.

Clinical Application 20.1: Pediatric Anesthetic Induction

The majority of pediatric patients under 12 years of age requiring a general anesthetic for surgery present to the operating room without an intravenous (IV) line. Induction of anesthesia can be achieved by placing a facemask over the patient's nose and mouth and using *sevoflurane* in high doses to anesthetize the patient until an IV is placed. *Sevoflurane* is the preferred inhalational anesthetic due to its low pungency and respiratory irritation. Flavoring can also be added to the mask to aid in the patient's cooperation. For short procedures, such as myringotomy tubes (ear tubes), the anesthesiologist can elect to not place an IV and keep the patient anesthetized by just masking with *sevoflurane* for the entirety of the procedure.

H. Nitrous oxide

Nitrous oxide [NYE-truss OX-ide] ("laughing gas") is a nonirritating potent sedative that is unable to create a state of general anesthesia. It is frequently used at concentrations of 30% to 50% in combination with oxygen to create moderate sedation, particularly in dentistry. *Nitrous oxide* does not depress respiration and maintains cardiovascular hemodynamics as well as muscular strength. *Nitrous oxide* can be combined with other inhalational agents to establish general anesthesia, which lowers the required concentration of the combined volatile agent. This gas admixture further reduces many unwanted side effects of the other volatile agents that impact cardiovascular output and cerebral blood flow. *Nitrous oxide* is poorly soluble in blood and other tissues, allowing

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it to move very rapidly in and out of the body. This can be problematic in closed body compartments because *nitrous oxide* can increase the volume (exacerbating a pneumothorax) or pressure (sinus or middle ear pressure); it replaces nitrogen in various air spaces faster than the nitrogen leaves. Its speed of movement allows *nitrous oxide* to retard oxygen uptake during emergence, thereby causing "diffusion hypoxia." This can be overcome by delivering high concentrations of inspired oxygen during emergence. Some characteristics of the inhalation anesthetics are summarized in Figure 20.9.

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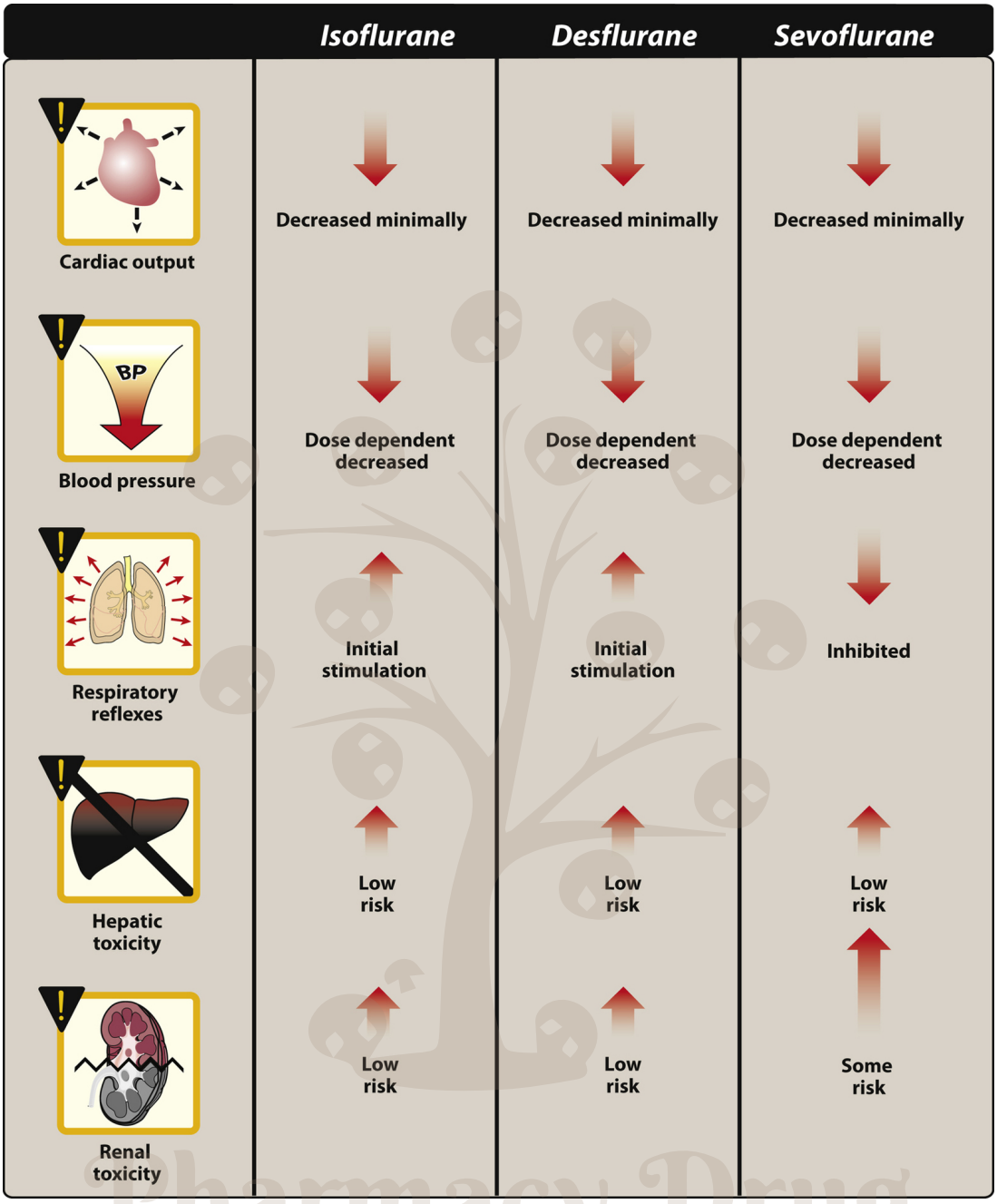

Figure 20.9 Characteristics of some inhalation anesthetics.

I. Malignant hyperthermia

In a very small percentage of susceptible patients, exposure to halogenated hydrocarbon anesthetics (or *succinylcholine*) may induce malignant hyperthermia (MH), a rare life-threatening

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condition. MH causes a drastic and uncontrolled increase in skeletal muscle oxidative metabolism, overwhelming the body's capacity to supply oxygen, remove carbon dioxide, and regulate temperature, eventually leading to circulatory collapse and death if not treated immediately. Strong evidence indicates that MH is due to an excitation–contraction coupling defect. Burn victims and individuals with muscular dystrophy, myopathy, myotonia, and osteogenesis imperfecta are susceptible to MH-like events, and caution should be taken when halogenated anesthetics are used. Susceptibility to MH is often inherited as an autosomal dominant disorder. Susceptibility can occur due to multiple genetic mutations, but the most common one is the ryanodine receptor 1 (RYR1) mutation. RYR1 is a skeletal muscle calcium release channel. Should a patient exhibit symptoms of MH, *dantrolene* is given as the anesthetic mixture is withdrawn, and measures are taken to rapidly cool the patient. *Dantrolene* [DAN-troe-leen] blocks release of Ca^{2+} from the sarcoplasmic reticulum of muscle cells, reducing heat production and relaxing muscle tone. It should be available whenever triggering agents such as halogenated anesthetics are administered. In addition, the patient must be monitored and supported for respiratory, circulatory, and renal problems. Use of *dantrolene* and avoidance of triggering agents in susceptible individuals have markedly reduced mortality from MH. A more soluble formulation of *dantrolene* has become commercially available that drastically reduces the time needed to prepare this drug in emergencies.

V. INTRAVENOUS ANESTHETICS

IV anesthetics cause rapid induction of anesthesia often occurring in 1 minute or less. It is the most common way to induce anesthesia before maintenance of anesthesia with an inhalation agent. IV anesthetics may be used as a single bolus for very short procedures or administered as TIVA to maintain sedation or general anesthesia during longer surgeries. In TIVA cases, typically a bolus of the

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induction drug (for example, *propofol*) is delivered to induce general anesthesia or sedation, and then a constant infusion of the IV anesthetic is titrated to the appropriate level of sedation. If doses of the TIVA are low enough, a lower level of sedation may be delivered and maintained, such as moderate or deep sedation (see Figure 20.3).

A. Induction

After entering the blood, a percentage of drug binds to plasma proteins, and the rest remains unbound or "free." The degree of protein binding depends upon the physical characteristics of the drug, such as the degree of ionization and lipid solubility. The majority of CO flows to the brain, liver, and kidney ("vessel-rich organs"). Thus, a high proportion of initial drug bolus is delivered to the cerebral circulation and then passes along a concentration gradient from blood into the brain. The rate of this transfer is dependent on the arterial concentration of the unbound free drug, the lipid solubility of the drug, and the degree of ionization. Unbound, lipid-soluble, nonionized molecules cross into the brain most quickly. Like inhalational anesthetics, the exact mode of action of IV anesthetics is unknown; however, GABA likely plays a prominent role.

B. Emergence

Emergence from IV anesthetics is due to redistribution from the CNS. After initial flooding of the CNS and other vessel-rich tissues with nonionized molecules, the drug diffuses into other tissues with less blood supply. With secondary tissue uptake, predominantly skeletal muscle, plasma concentration of the drug falls. This allows the drug to diffuse out of the CNS, down the resulting reverse concentration gradient. This initial redistribution of drug into other tissues leads to the rapid recovery seen after a single IV dose of induction agent. Metabolism and plasma clearance become important only following infusions and repeat doses of a drug. Adipose tissue makes little contribution to the early redistribution of free drug following a bolus, due to its poor

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blood supply. However, following repeat doses or infusions, equilibration with fat tissue forms a drug reservoir, often leading to delayed emergence.

C. Effect of reduced cardiac output on IV anesthetics

When CO is reduced (for example, in certain types of shock, the elderly, cardiac disease), the body compensates by diverting more CO to the cerebral circulation. A greater proportion of the IV anesthetic enters the cerebral circulation under these circumstances. Therefore, the dose of the drug must be reduced. Furthermore, decreased CO causes prolonged circulation time. As global CO is reduced, it takes a longer time for an induction drug to reach the brain and exert its effects. **The slow titration of a reduced dose of an IV anesthetic is key to a safe induction in patients with reduced CO.**

D. Propofol

Propofol [PROE-poe-fol] is an IV sedative/hypnotic used for induction and/or maintenance of anesthesia. It is widely used and has replaced *thiopental* as the first choice for induction of general anesthesia and sedation. Because *propofol* is poorly water soluble, it is supplied as an emulsion containing soybean oil and egg phospholipid, giving it a milk-like appearance.

1.Onset: Induction is smooth and occurs 30 to 40 seconds after administration. Plasma levels decline rapidly as a result of redistribution, followed by a more prolonged period of hepatic metabolism and renal clearance. The initial redistribution half-life is 2 to 4 minutes. The pharmacokinetics of *propofol* are not altered by moderate hepatic or renal failure.

2.Actions: Although *propofol* depresses the CNS, it occasionally contributes to excitatory phenomena, such as muscle twitching, spontaneous movement, yawning, and hiccups. Transient pain at the injection site is common. *Propofol* decreases blood pressure without significantly

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depressing the myocardium. It also reduces intracranial pressure, mainly due to decreased cerebral blood flow and oxygen consumption. It has less of a depressant effect than volatile anesthetics on CNS-evoked potentials, making it useful for surgeries in which spinal cord function is monitored. It does not provide analgesia, so supplementation with opioids is required. *Propofol* is commonly infused in lower doses to provide sedation. The incidence of postoperative nausea and vomiting (PONV) is very low secondary to its antiemetic properties.

E. Barbiturates

Thiopental [THYE-oh-PEN-tahl] is an ultra–short-acting barbiturate with high lipid solubility. It is a potent anesthetic but a weak analgesic. Barbiturates require supplementary analgesic administration during anesthesia. When given IV, agents such as *thiopental* and *methohexital* [meth-oh-HEX-uh-tall] quickly enter the CNS and depress function, often in less than 1 minute. However, diffusion out of the brain can also occur very rapidly because of redistribution to other tissues (Figure 20.10). These drugs may remain in the body for relatively long periods, because only about 15% of a dose entering the circulation is metabolized by the liver per hour. Thus, metabolism of *thiopental* is much slower than its redistribution. Barbiturates tend to decrease blood pressure, which may cause a reflex tachycardia. They decrease intracranial pressure through reductions in cerebral blood flow and oxygen consumption. *Thiopental* is no longer available in many countries, including the United States. *Methohexital* is still commonly used for electroconvulsive therapy because unlike all other barbiturates, it lowers the seizure threshold.

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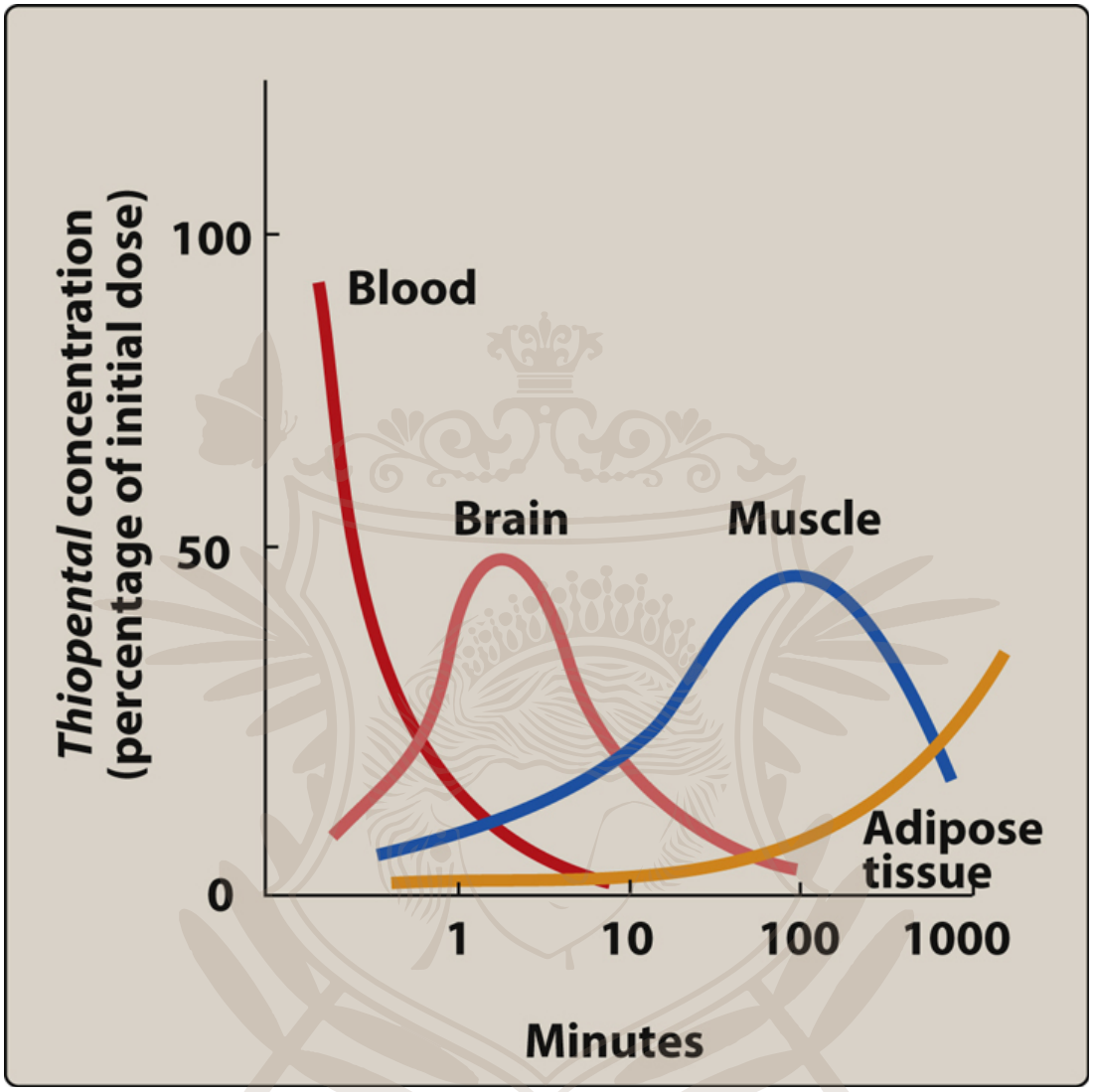

Figure 20.10 Redistribution of *thiopental* from the brain to muscle and adipose tissue.

F. Benzodiazepines

The benzodiazepines are used in conjunction with anesthetics for sedation and amnesia. The most commonly used is *midazolam* [meh-DAZ-o-lam]. *Diazepam* [dye-AZ-uh-pam] and *lorazepam* [lore-AZ-uh-pam] are alternatives. All three facilitate amnesia while causing sedation by enhancing the inhibitory effects of various neurotransmitters such as GABA. Minimal cardiovascular depressant effects are seen, but all are potential respiratory

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depressants (especially when administered IV). They are metabolized by the liver with variable elimination half-lives. *Midazolam* is a CYP3A4 substrate, and strong inhibitors of CYP3A4 (for example, *clarithromycin* and *erythromycin*) may prolong effects of *midazolam.* Benzodiazepines can induce a temporary form of anterograde amnesia in which the patient retains memory of past events, but new information is not transferred into long-term memory. Therefore, important treatment information should be repeated to the patient after the effects of the drug have worn off.

G. Opioids

Because of their analgesic properties, opioids are commonly combined with other anesthetics. The choice of opioid is based primarily on the duration of action needed. The most commonly used opioids are *fentanyl* [FEN-ta-nil] and its congeners, *sufentanil* [soo-FEN-ta-nil], and *remifentanil* [rem-i-FEN-ta-nil], because they induce analgesia more rapidly than *morphine.* They may be administered intravenously, epidurally, or intrathecally (into the cerebrospinal fluid). Opioids are not amnestic without synergistic drug administration, and they can all cause hypotension and respiratory depression, along with nausea and vomiting. Opioid effects can be antagonized by *naloxone.* See Chapter 21 for detailed information on the opioids.

H. Etomidate

Etomidate [ee-TOM-uh-date] is a hypnotic agent used to induce anesthesia, but it lacks analgesic activity. Its water solubility is poor, so it is formulated in a propylene glycol solution. Induction is rapid, and the drug is short acting. A key benefit of *etomidate* is hemodynamic stability, since this agent has minimal impact on cardiac output and systemic vascular resistance. *Etomidate* is usually only used for patients with cardiovascular dysfunction or patients who are acutely critically ill. It inhibits 11-β hydroxylase involved in steroidogenesis, and adverse effects may include decreased plasma cortisol and aldosterone levels. *Etomidate*

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should not be infused for an extended time, because prolonged suppression of these hormones is dangerous. Injection site pain, involuntary skeletal muscle movements, and nausea and vomiting are common.

I. Ketamine

Ketamine [KET-uh-meen], a short-acting anti-NMDA receptor anesthetic and analgesic, induces a dissociated state in which the patient appears disconnected from the external environment while experiencing profound analgesia; however, their level of consciousness is not readily identifiable. *Ketamine* stimulates central sympathetic outflow, causing stimulation of the heart with increased blood pressure and CO. It is also a potent bronchodilator. Therefore, it is beneficial in patients with hypovolemic or cardiogenic shock as well as asthmatics. Conversely, it is contraindicated in hypertensive or stroke patients. The drug is lipophilic and enters the brain very quickly. Like the barbiturates, it redistributes to other organs and tissues. *Ketamine* has become popular as an adjunct to reduce opioid consumption during surgery. Of note, it may induce hallucinations and dysphoria, particularly in young adults, but pretreatment with benzodiazepines may help. *Ketamine* may be used illicitly, since it causes a dreamlike state and hallucinations similar to *phencyclidine*.

J. Dexmedetomidine

Dexmedetomidine [dex-med-eh-TOM-uh-deen] is a sedative used in intensive care settings and surgery. Like *clonidine*, it is an α_2 receptor agonist in certain parts of the brain. *Dexmedetomidine* has sedative, analgesic, sympatholytic, and anxiolytic effects that blunt many cardiovascular responses. It reduces volatile anesthetic, sedative, and analgesic requirements without causing significant respiratory depression and can be used as the sole agent for TIVA. It has gained popularity for its ability to blunt emergence delirium in the pediatric population. Some therapeutic

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advantages and disadvantages of the anesthetic agents are summarized in Figure 20.11.

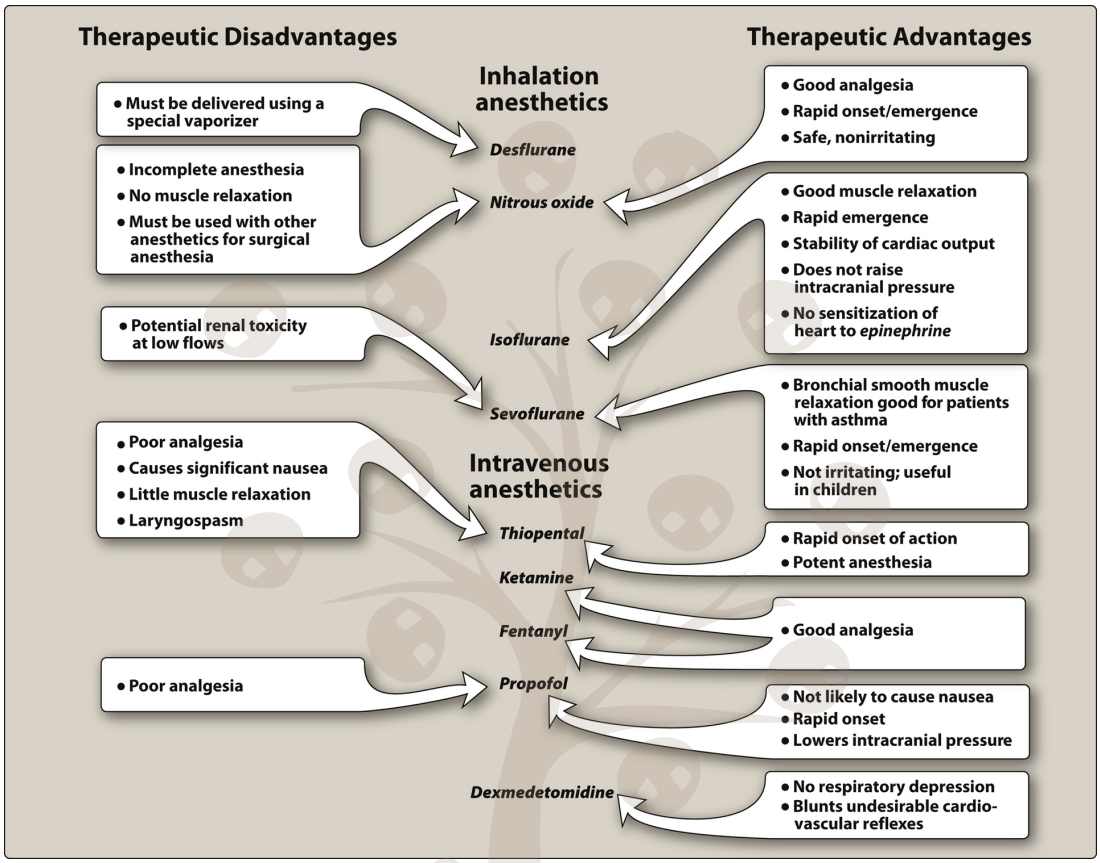

Figure 20.11 Therapeutic disadvantages and advantages of some anesthetic agents.

VI. NEUROMUSCULAR BLOCKERS

Neuromuscular blockers are crucial to the practice of anesthesia and used to facilitate endotracheal intubation and provide muscle relaxation when needed for surgery. Their mechanism of action is via blockade of nicotinic acetylcholine receptors on the skeletal muscle cell membrane. These agents include *cisatracurium*, *mivacurium*,

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pancuronium, *rocuronium*, *succinylcholine*, and *vecuronium* (see Chapter 5).

A. Sugammadex

Sugammadex [soo-GAM-ma-dex] is a selective relaxant-binding agent that terminates the action of both *rocuronium* and *vecuronium.* Its three-dimensional structure traps the neuromuscular blocker in a 1:1 ratio, terminating its action and making it water soluble. It is unique in that it produces rapid and effective reversal of both shallow and profound neuromuscular blockade. *Sugammadex* is eliminated via the kidneys.

VII. LOCAL ANESTHETICS

Local anesthetics block nerve conduction of sensory impulses and in higher concentrations block motor impulses from the periphery to the CNS. Sodium ion channels are blocked to prevent the transient increase in permeability of the nerve membrane to Na^+ that is required for an action potential (Figure 20.12). When propagation of action potentials is prevented, sensation cannot be transmitted from the source of stimulation to the brain. Delivery techniques include topical administration, infiltration, and perineural and neuraxial (spinal, epidural, or caudal) blocks. Small, unmyelinated nerve fibers for pain, temperature, and autonomic activity are most sensitive. Structurally, local anesthetics all include a lipophilic group joined by an amide or ester linkage to a carbon chain, which, in turn, is joined to a hydrophilic group (Figure 20.13). The most widely used local anesthetics are *bupivacaine* [byoo-PIV-uh-cane], *lidocaine* [LYE-doe-cane], *mepivacaine* [muh-PIV-uh-cane], *ropivacaine* [roe-PIV-uh-cane], *chloroprocaine* [klor-oh-PROE-cane], and *tetracaine* [TET-truh-cane].

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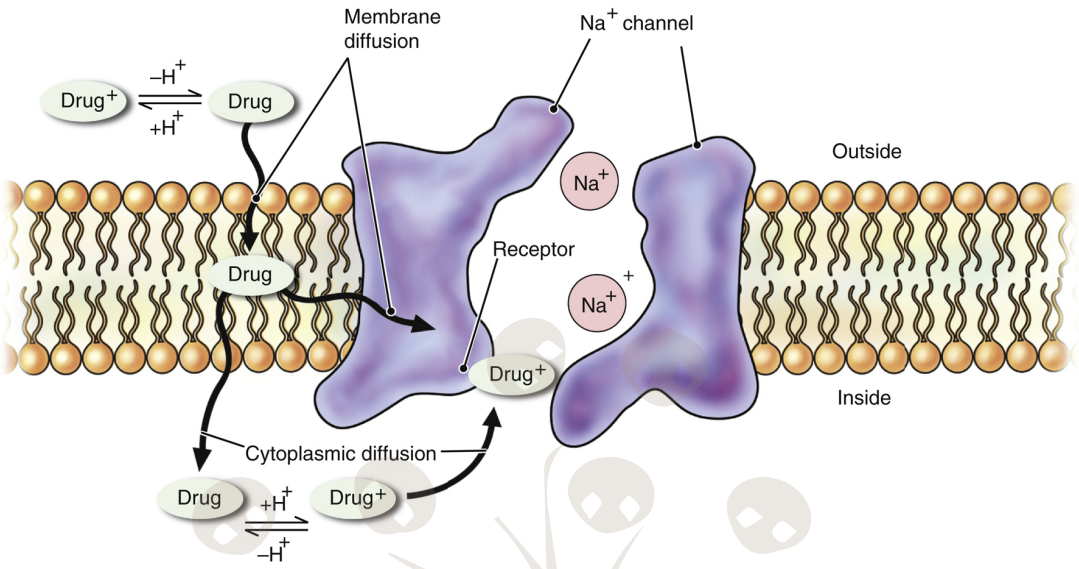

Figure 20.12 Mechanism of local anesthetic action.

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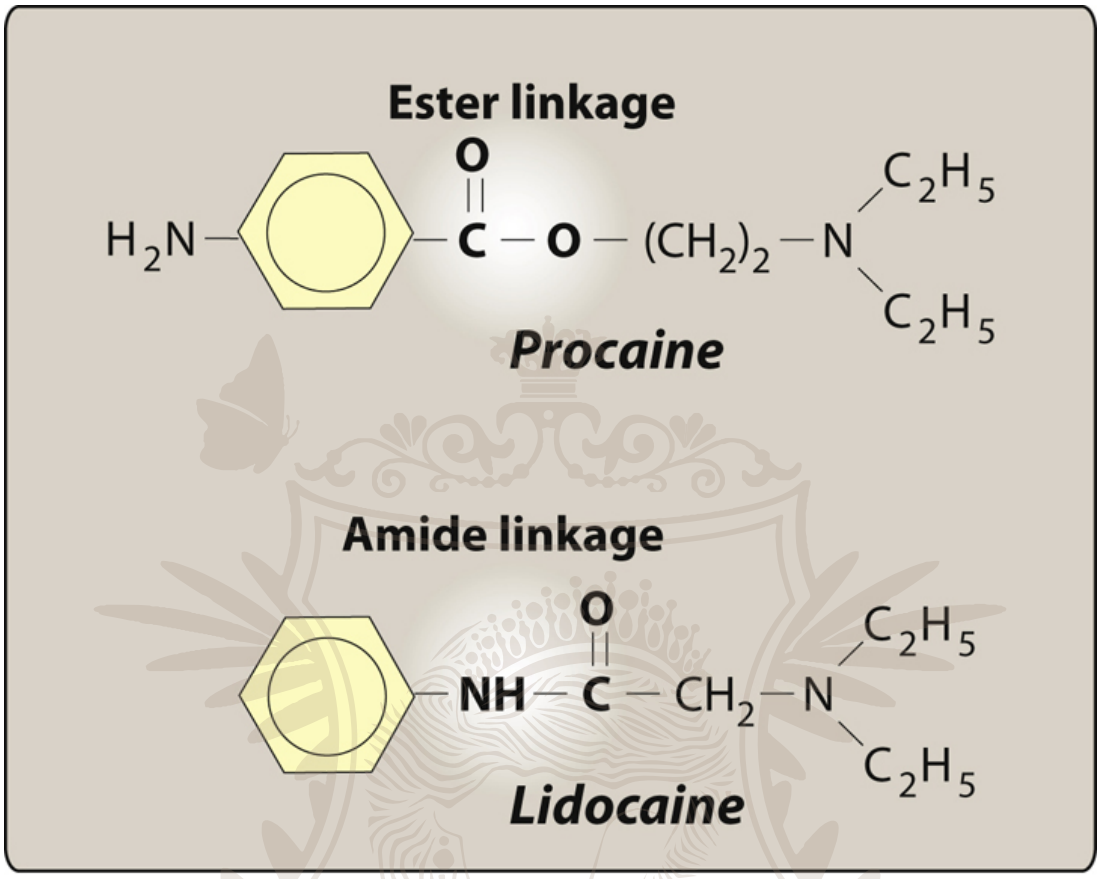

Figure 20.13 Representative structures of ester and amide anesthetics.

A. Actions

Local anesthetics cause vasodilation (with the exception of *cocaine*), which leads to a rapid diffusion away from the site of action and short duration when these drugs are administered alone. By adding the vasoconstrictor *epinephrine*, the rate of local anesthetic absorption and diffusion is decreased. This minimizes systemic toxicity and increases the duration of action. Hepatic function does not affect the duration of action of local anesthesia because that is determined by redistribution rather than biotransformation. Some local anesthetics have other therapeutic uses (for example, *lidocaine* is an IV antiarrhythmic; see Chapter 11).

B. Onset, potency, and duration of action

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The onset of action of local anesthetics is influenced by several factors including tissue pH, nerve morphology, concentration, pKa, and lipid solubility of the drug. Of these, the pKa is most important. Local anesthetics with a lower pKa have a quicker onset, since more drug exists in the unionized form at physiologic pH, thereby allowing penetration of the nerve cell membrane. Once at the nerve membrane, the ionized form interacts with the protein receptor of the Na^+ channel to inhibit its function and achieve local anesthesia. The pH of surrounding tissues may decrease during active infections causing onset of local anesthetic to be delayed or even prevented. Potency and duration of these agents depend mainly on lipid solubility, with higher solubility correlating with increased potency and duration of action.

C. Metabolism

Biotransformation of amides occurs primarily in the liver. *Prilocaine* [PRY-low-cane], a dental anesthetic, is also metabolized in the plasma and kidney, and one of its metabolites may lead to methemoglobinemia. Esters are biotransformed by plasma cholinesterase (pseudocholinesterase). Patients with pseudocholinesterase deficiency may metabolize ester local anesthetics more slowly. At normal doses, this has little clinical effect. Reduced hepatic function predisposes patients to toxic effects but should not significantly increase the duration of action of local anesthetics.

D. Allergic reactions

Patient reports of allergic reactions to local anesthetics are fairly common, but often times, reported “allergies” are actually side effects from the coadministered *epinephrine.* True allergy to an amide local anesthetic is exceedingly rare, while the ester *procaine* is more allergenic and has largely been removed from the market. Allergy to one ester rules out use of another ester because the allergenic component is the metabolite para-aminobenzoic acid produced by all esters. By contrast, allergy to one amide does not rule out the use of another amide. A patient

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may be allergic to other compounds in the local anesthetic, such as preservatives in multidose vials.

E. Local anesthetic systemic toxicity

Toxic blood levels of a local anesthetic may be due to repeated injections or could result from a single inadvertent IV injection. Each drug has a weight-based toxic threshold that should be calculated. This is especially important in children, the elderly, and women in labor (who are more susceptible to local anesthetics). Aspiration before every injection is imperative. The signs, symptoms, and timing of local anesthetic systemic toxicity (LAST) are unpredictable. One must consider the diagnosis in any patient with altered mental status, seizures, or cardiovascular instability following injection of local anesthetic. Treatment for LAST may include antiseizure drugs, airway management, and cardiopulmonary support. Administering a 20% lipid emulsion infusion (lipid rescue therapy) is a valuable asset. Figure 20.14 summarizes pharmacologic properties of some local anesthetics.

CHARACTERISTIC	ESTERS • *Benzocaine* • *Procaine* • *Chloroprocaine* • *Tetracaine* • *Cocaine*	AMIDES • *Bupivacaine* • *Prilocaine* • *Lidocaine* • *Ropivacaine* • *Mepivacaine*
Metabolism	Rapid by plasma cholinesterase	Slow, hepatic
Systemic toxicity	Less likely	More likely
Allergic reaction	Possible—PABA derivatives form	Very rare
Stability in solution	Breaks down in ampules (heat, sun)	Very stable chemically
Onset of action	Slow as a general rule	Moderate to fast
pKa	Higher than physiologic pH (8.5–8.9)	Close to physiologic pH (7.6–8.1)

DRUG	POTENCY	ONSET	DURATION
Bupivacaine	High	Slow	Long
Chloroprocaine	Low	Rapid	Short
Lidocaine	Low	Rapid	Intermediate
Mepivacaine	Low	Moderate	Intermediate
Ropivacaine	High	Moderate	Long
Tetracaine	High	Slow	Long (spinal)

Figure 20.14 Summary of pharmacologic properties of some local anesthetics.PABA = para-aminobenzoic acid.

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VIII. ANESTHETIC ADJUNCTS

Adjuncts are a critical part of the practice of anesthesia and include drugs that affect gastrointestinal (GI) motility, PONV, anxiety, and analgesia. Adjuncts are used in collaboration to help make the anesthetic experience safe and pleasant.

A. Gastrointestinal agents

H_2-receptor antagonists (for example, *famotidine*; see Chapter 42) and proton pump inhibitors (for example, *omeprazole*; see Chapter 42) help to reduce gastric acidity in the event of an aspiration. Nonparticulate antacids (*sodium citrate*/*citric acid*) are given occasionally to quickly increase the pH of stomach contents in order to reduce the consequences of an unintentional aspiration. These drugs are used in the obstetric population going to surgery, along with other patients with reflux. Finally, a dopamine receptor antagonist (*metoclopramide*) can be used as a prokinetic agent to speed gastric emptying and increase lower esophageal sphincter tone to further reduce the risk of aspiration.

B. Drugs for PONV

PONV can be a significant problem during and after surgery both for the clinician and the patient. Risk factors for PONV include female gender, nonsmoker, use of volatile and nitrous anesthetics, duration of surgery, and postoperative narcotic use. 5-HT_3 receptor antagonists (for example, *ondansetron*; see Chapter 42) are commonly used to prevent PONV and are usually administered toward the end of surgery. These agents should be used with caution in patients with long QT intervals, and electrocardiogram monitoring is needed. An anticholinergic and antihistamine (*promethazine*) can also be used; however, sedation, delirium, and confusion can complicate the postoperative period, especially in the elderly. Glucocorticoids such as *dexamethasone* can be used to reduce PONV. The mechanism is unclear, but because of a longer onset, these

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agents are usually given at the start of surgery. Lastly, transdermal *scopolamine* is given preoperatively to patients with multiple risk factors or a history of PONV. Caution is advised because it can produce central anticholinergic effects. The avoidance of volatile agents and use of *propofol* TIVA can greatly reduce the incidence of PONV.

C. Anxiolytics

Anxiety is a common part of the surgical experience. Benzodiazepines (*midazolam*, *diazepam*), α_2 agonists (*clonidine*, *dexmedetomidine*), and H_1-receptor antagonists (*diphenhydramine*) can be used to alleviate anxiety. Benzodiazepines also elicit anterograde amnesia, which can help promote a more pleasant surgical experience by eliminating memories leading up to emergence.

Clinical Application 20.2: Postoperative Nausea

Postoperative nausea is one of the leading causes of patient dissatisfaction after anesthesia and also leads to longer postoperative stays at outpatient surgery centers. In addition to medications for nausea such as *ondansetron* and *promethazine*, avoidance of anesthetics likely to trigger nausea is another strategy to reduce PONV. Instead of using inhalational anesthetics for maintenance of anesthesia, maintenance can be achieved via TIVA using *propofol.* As discussed above, *propofol* has antiemetic properties, and in conjunction with medications such as *ondansetron*, *promethazine*, and *dexamethasone*, multiple nausea receptors can be blocked while avoiding nausea-provoking anesthetics. A transdermal *scopolamine* patch can also be added preoperatively for best results.

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D. Analgesia

While opioids are a mainstay in anesthesia for pain control, multimodal analgesia is becoming more common due to the long-term risks of opioid consumption in surgical patients. Nonsteroidal anti-inflammatory drugs (*ketorolac*, *celecoxib*; see Chapter 40) are common adjuncts to opioids. Caution should be used in patients

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with coagulopathies, and in those with a history of peptic ulcer or platelet aggregation abnormalities. *Acetaminophen* can be used both PO and IV, but caution is advised in impaired hepatic function. Analogs of GABA (*gabapentin*, *pregabalin*; see Chapter 19) are becoming more common as pretreatment to reduce opioid consumption both during and after surgery. They also have multiple uses in neuropathic pain and addiction medicine. The NMDA antagonist *ketamine* is used to reduce overall opioid consumption both intra- and postoperatively. Actions of anesthesia adjunct drugs are shown in Figure 20.15.

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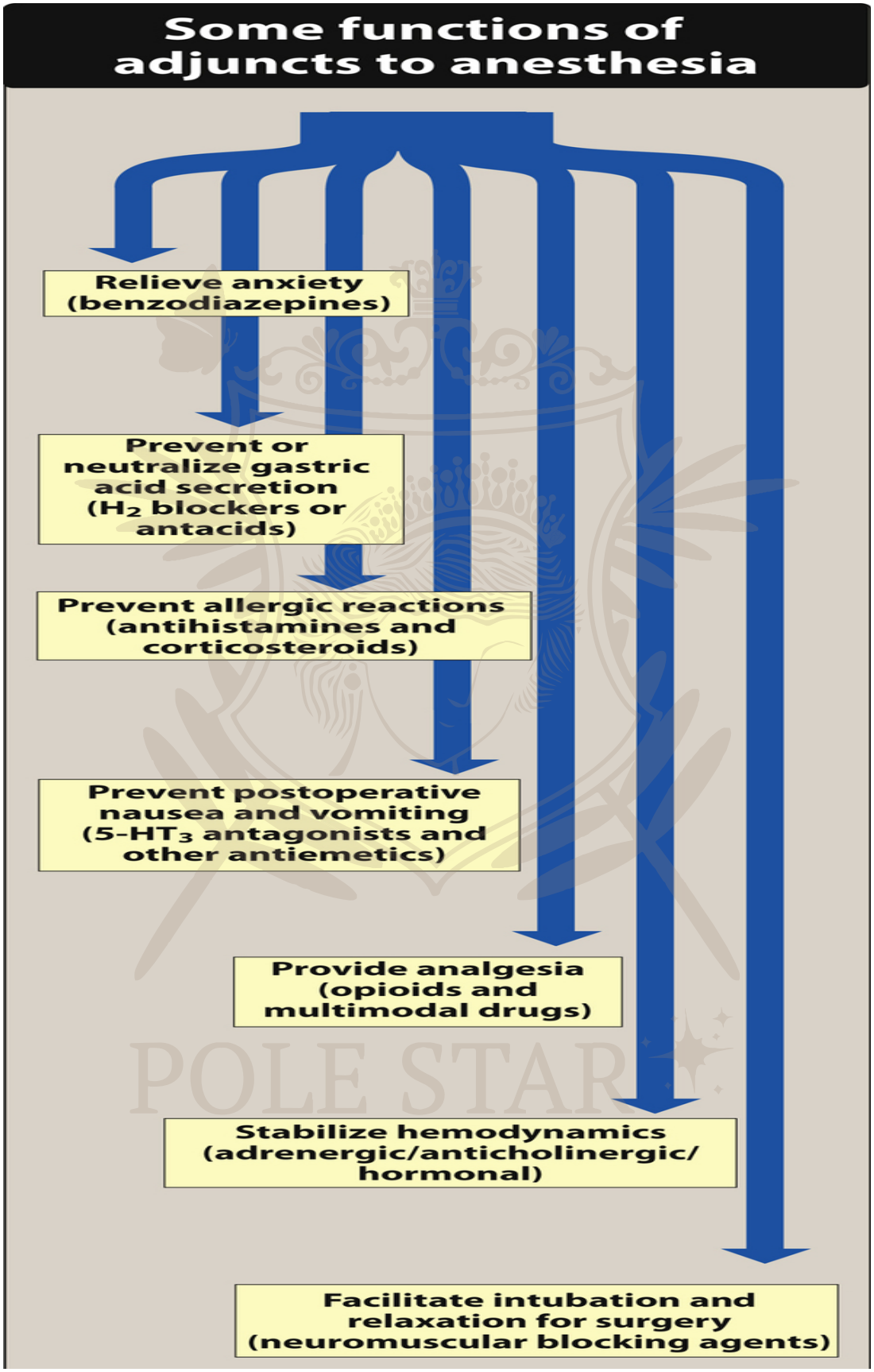
Some functions of adjuncts to anesthesia
Relieve anxiety (benzodiazepines)
Prevent or neutralize gastric acid secretion (H_2 blockers or antacids)
Prevent allergic reactions (antihistamines and corticosteroids)
Prevent postoperative nausea and vomiting ($5\text{-}HT_3$ antagonists and other antiemetics)
Provide analgesia (opioids and multimodal drugs)
Stabilize hemodynamics (adrenergic/anticholinergic/ hormonal)
Facilitate intubation and relaxation for surgery (neuromuscular blocking agents)

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Figure 20.15 Actions of anesthesia adjunct drugs.

Chapter Summary

- The levels of sedation occur in a dose-related continuum, which is variable and depends on individual patient response to various drugs. These "artificial" levels of sedation start with light sedation (anxiolysis) and continue to moderate sedation, then deep sedation, and finally a state of general anesthesia.
- General anesthesia is a reversible state of central nervous system (CNS) depression, causing loss of response to and perception of stimuli. The state of general anesthesia can be divided into three stages: induction, maintenance, and emergence.
- Inhaled gases are used primarily for maintenance of anesthesia after administration of an IV anesthetic. Modern inhalational anesthetics are nonflammable, nonexplosive agents, which include *nitrous oxide* and volatile, halogenated hydrocarbons such as *isoflurane*, *sevoflurane*, and *desflurane.*
- Potency is defined quantitatively as the minimum alveolar concentration (MAC), which is the end-tidal concentration of inhaled anesthetic needed to eliminate movement in 50% of patients exposed to a noxious stimulus.
- The principal objective of inhalation anesthesia is a constant and optimal brain partial pressure of inhaled anesthetic. The time course for attaining this steady state is determined by alveolar wash-in, anesthetic uptake, and washout. No specific receptor has been identified as the locus to create a state of general anesthesia, and it appears that a variety of molecular mechanisms may contribute to the activity of anesthetics.
- Malignant hyperthermia is a rare, life-threatening condition that can occur with halogenated hydrocarbon anesthetics or *succinylcholine.* The condition causes a drastic increase in skeletal muscle oxidative metabolism, and it can be effectively treated with *dantrolene.*
- Intravenous anesthetics cause rapid induction of anesthesia, with emergence due to redistribution from the CNS. *Propofol*, *methohexital*, *etomidate*, and *ketamine* are all common intravenous anesthetics.
- The mechanism of action of neuromuscular blockers is via blockade of nicotinic acetylcholine receptors on the skeletal muscle cell membrane. *Sugammadex* is a selective relaxant-binding agent that produces rapid reversal of the neuromuscular blockers *rocuronium* and *vecuronium.*

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- Local anesthetics block nerve conduction of sensory impulses and in higher concentrations block motor impulses from the periphery to the CNS via sodium channel inhibition. Local anesthetic systemic toxicity (LAST) can occur when toxic thresholds are reached and should be treated with lipid emulsion therapy.
- Anesthetic adjuncts are a critical part of the practice of anesthesia and include drugs that affect gastrointestinal motility, PONV, anxiety, and analgesia.

STUDY QUESTIONS

Choose the ONE best answer.

20.1 Regarding levels of sedation, which of the following indicates having some response to stimuli, but respirations may be inadequate?

A. Anxiolysis
B. General anesthesia
C. Moderate sedation
D. Deep sedation

Correct answer = D. Anxiolysis is a state of relaxation, but consciousness remains. General anesthesia is a total loss of perception and sensation to stimuli. Moderate sedation maintains mentation with adequate airway and respiratory competency. Deep sedation has some response to stimuli, but respirations may be inadequate.

20.2 Which of the following decreases minimum alveolar concentration (MAC)?

A. Hyperthermia
B. Cocaine intoxication
C. Chronic ethanol abuse
D. Acute ethanol intoxication

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Correct answer = D. Acute ethanol intoxication is the only choice that decreases minimum alveolar concentration. All the other options increase MAC.

20.3 Which of the following determines the speed of recovery from intravenous anesthetics used for induction?

A. Liver metabolism of the drug
B. Redistribution of the drug from sites in the CNS
C. Ionization of the drug
D. Protein binding of the drug

Correct answer = B. Following initial flooding of the CNS with nonionized molecules, the drug diffuses into other tissues. With secondary tissue uptake, the plasma concentration falls, allowing the drug to diffuse out of the CNS. This initial redistribution of drug into other tissues leads to the rapid recovery seen after a single dose of an IV induction drug. Protein binding, ionization, and lipid solubility affect the rate of transfer.

20.4 A 32-year-old woman with a history of severe postoperative nausea and vomiting is coming in for plastic surgery. Which of the following anesthetic drugs would be best to use for maintenance in this situation?

A. Isoflurane
B. Propofol
C. Nitrous oxide
D. Sevoflurane

Correct answer = B. A propofol infusion (TIVA) anesthetic would be best for this patient with a history of postoperative nausea and vomiting. Propofol is the only anesthetic listed with antiemetic properties. Both halogenated hydrocarbons (isoflurane and sevoflurane) and nitrous oxide are linked to nausea and vomiting during surgery.

20.5 A 65-year-old patient in the intensive care unit needs sedation due to prolonged endotracheal intubation after an

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exploratory laparotomy. Which of the following drugs should be avoided for sedation in this patient?

A. Etomidate
B. Fentanyl
C. Propofol
D. Dexmedetomidine

Correct answer = A. Adverse effects of etomidate include decreased plasma cortisol and aldosterone levels by inhibiting the 11-β hydroxylase enzyme. Etomidate should not be infused for an extended time, because prolonged suppression of these hormones is dangerous. All of the other choices could be used for sedation in the intensive care unit setting.

20.6A 20-year-old man presents with appendicitis and requires a surgical intervention. He has a family history of malignant hyperthermia. Which of the following anesthetic drugs should be avoided in this patient?

A. Isoflurane
B. Propofol
C. Midazolam
D. Fentanyl

Correct answer = A. All halogenated hydrocarbons (isoflurane, sevoflurane, desflurane) as well as succinylcholine are contraindicated and considered triggering agents. Flushing of the anesthesia machine, removal of vaporizers, use of special filters, and availability of dantrolene are highly advised. Propofol as well as anxiolytics (midazolam) and opioids (fentanyl) are safe in malignant hyperthermia.

POLE STAR

20.7A 32-year-old woman presents for a right distal radius fracture. She requests regional anesthesia to help with her pain postoperatively. She reports that, as a child, she had an allergic reaction to Novocain (procaine) at the dentist's office. Which of the following local anesthetics should be avoided in this patient?

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A. Mepivacaine
B. Bupivacaine
C. Ropivacaine
D. Tetracaine

Correct answer = D. Procaine is an ester local anesthetic. Since this patient has an allergy to procaine, other ester anesthetics (chloroprocaine, tetracaine, benzocaine) should not be used. All other options are amide local anesthetics commonly used in regional anesthesia to facilitate peripheral nerve blockade.

20.8 A 3-year-old girl presents for removal of tonsils and adenoids. She does not have an IV placed preoperatively. Which of the following is the most appropriate choice of anesthetic for induction of anesthesia?

A. Isoflurane
B. Desflurane
C. Sevoflurane
D. Propofol

Correct answer = C. Sevoflurane has low pungency and respiratory irritation compared with isoflurane and desflurane and is preferred for inhalational anesthetic inductions in pediatrics. Propofol requires an IV for anesthetic induction.

20.9 A 12-year-old boy presents for a right distal radius fracture closed reduction in the emergency department. Which of the following anesthetics would be best to provide both amnesia and analgesia for this patient?

A. Ketamine
B. Propofol
C. Midazolam
D. Fentanyl

Correct answer = A. Ketamine is unique in its blockage of NMDA receptors, yielding both potent anesthetic and analgesic properties. Benzodiazepines such

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as midazolam have little analgesic effect but can be a potent anesthetic at high doses. Fentanyl is a potent analgesic. Propofol is a potent anesthetic but a weak analgesic commonly used for the induction of anesthesia.

20.10 A 45-year-old man is undergoing a laparoscopic appendectomy with general anesthesia. After induction of anesthesia and administration of rocuronium, the patient is not able to be intubated and needs to have the paralytic reversed. Which of the following is the most appropriate drug for this situation?

A. Propofol
B. Midazalam
C. Sugammadex
D. Fentanyl

Correct answer = C. Sugammadex is a selective relaxant-binding agent with a three-dimensional structure that traps the neuromuscular blocker and terminates its action. It produces rapid and effective reversal of both shallow and profound neuromuscular blockade. All the other options do not reverse muscle relaxants.

POLE STAR

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21

Opioids

Robin Moorman Li, Matthew G. Hermenau

I. OVERVIEW

Management of pain is one of clinical medicine's greatest challenges. The International Association for the Study of Pain (IASP) currently defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." Pain can be either acute or chronic and is subjective, being influenced to varying degrees by biological, psychological, and social factors. The clinician must rely on the patient's perception and description of pain when crafting a therapeutic regimen. Alleviation of pain depends on the specific type of pain (nociceptive, neuropathic, or central pain). For example, with mild to moderate arthritic pain (nociceptive pain), nonopioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs; see Chapter 40) are often effective. Neuropathic pain responds best to anticonvulsants, tricyclic antidepressants (TCAs), or serotonin/norepinephrine reuptake inhibitors (SNRIs). For severe acute pain or chronic malignant or nonmalignant pain, opioids can be considered as part of the treatment plan in select patients (Figure 21.1). Opioids are natural, semisynthetic, or synthetic compounds that produce *morphine*-like effects (Figure 21.2). These agents are divided into chemical classes based on their chemical structure (Figure 21.3). All opioids act by binding to specific opioid receptors in the central nervous system (CNS) to produce effects that mimic the action of endogenous peptide neurotransmitters (for example, endorphins, enkephalins, and dynorphins). Although the opioids have a broad range of effects, their primary use is to relieve intense pain that results from surgery, injury, or chronic disease. Unfortunately, widespread availability of opioids has led to abuse of agents with euphoric properties.

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Antagonists that reverse the actions of opioids are also clinically important for use in cases of overdose (Figure 21.1).

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STRONG AGONISTS

Alfentanil ALFENTA
Fentanyl ACTIQ, DURAGESIC, FENTORA, LAZANDA, SUBLIMAZE, SUBSYS
Heroin GENERIC ONLY
Hydrocodone HYSINGLA ER, ZOHYDRO ER
Hydromorphone DILAUDID
Levorphanol GENERIC ONLY
Meperidine DEMEROL
Methadone METHADOSE
Morphine KADIAN, MS CONTIN
Oxycodone ENDOCET*, OXAYDO, OXYCONTIN, PERCOCET*, ROXICODONE, XTAMPZA ER
Oxymorphone GENERIC ONLY
Remifentanil ULTIVA
Sufentanil DSUVIA, SUFENTA

MODERATE/LOW AGONISTS

Codeine GENERIC ONLY

MIXED AGONIST-ANTAGONISTS AND PARTIAL AGONISTS

Buprenorphine BELBUCA, BUPRENEX, BUTRANS
Butorphanol GENERIC ONLY
Nalbuphine GENERIC ONLY
Pentazocine GENERIC ONLY

ANTAGONISTS

Naloxone NARCAN
Naltrexone VIVITROL

OTHER ANALGESICS

Oliceridine OLINVYK
Tapentadol NUCYNTA
Tramadol CONZIP, QDOLO, ULTRAM, ULTRACET*

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Figure 21.1 Summary of opioid analgesics and antagonists with common trade names.* = Contains *acetaminophen*.

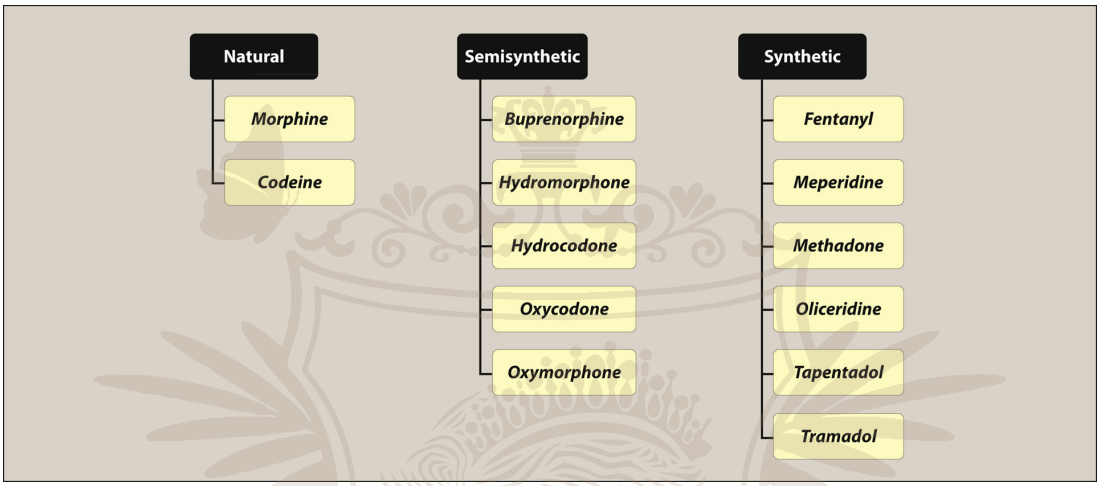

Figure 21.2 Origin of opioids: natural, semisynthetic, or synthetic.

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Phenanthrenes	Action on Opioid Receptors
Morphine	Agonist
Codeine	Agonist
Oxycodone	Agonist
Oxymorphone	Agonist
Hydromorphone	Agonist
Hydrocodone	Agonist
Levorphanol	Agonist
Buprenorphine	Partial agonist/Antagonist
Nalbuphine	Mixed Agonist/Antagonist
Butorphanol	Mixed Agonist/Antagonist
Naloxone	Antagonist
Naltrexone	Antagonist
Benzomorphans	
Pentazocine	Mixed Agonist/Antagonist
Phenylpiperidines	
Fentanyl	Agonist
Alfentanil	Agonist
Remifentanil	Agonist
Sufentanil	Agonist
Meperidine	Agonist
Diphenylheptanes	
Methadone	Agonist
Phenylpropylamines	
Tramadol	Agonist
Tapentadol	Agonist

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Figure 21.3 Pharmacological classes of opioids and actions on opioid receptors.

II. OPIOID RECEPTORS

The major effects of the opioids are mediated by three main receptor families, commonly designated as μ (mu, MOP), κ (kappa, KOP), and δ (delta, DOP). Each receptor family exhibits a different specificity for the drug(s) it binds. Additionally, there is the nociceptin (NOP) receptor, also referred to as ORL1, which has a similar structure to the three main receptors but does not bind classical opioid ligands. It is activated by its unique endogenous ligand and other agonists (for example, *buprenorphine*) and is still being investigated for treatment of pain, depression, and substance abuse. The analgesic properties of the opioids are primarily mediated by the μ receptors that modulate responses to thermal, mechanical, and chemical nociception. The κ receptors in the dorsal horn also contribute to analgesia by modulating the response to chemical and thermal nociception. The enkephalins interact more selectively with δ receptors in the periphery. All three opioid receptors are members of the inhibitory G protein–coupled receptor family and inhibit adenylyl cyclase production, resulting in a decrease in intracellular cyclic adenosine monophosphate (cAMP) levels. They are also associated with ion channels, increasing postsynaptic K^+ efflux (hyperpolarization) or reducing presynaptic Ca^{2+} influx, thus impeding neuronal firing and transmitter release in the spinal dorsal horn (Figure 21.4).

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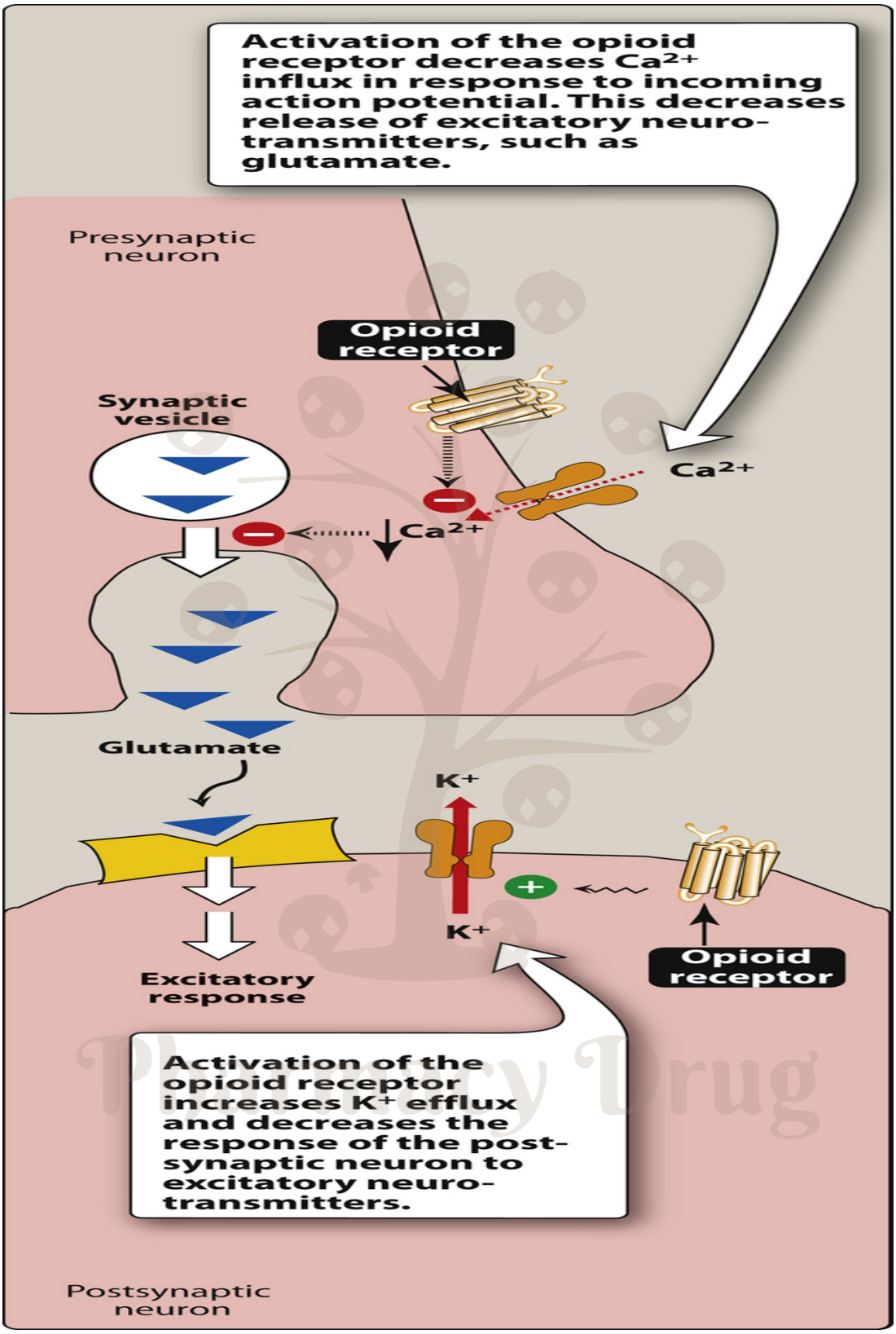

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Figure 21.4 Mechanism of action of μ opioid receptor agonists in the spinal cord.

III. OPIOID AGONISTS

Morphine [MOR-feen] is the prototypical μ receptor agonist. *Codeine* [KOE-deen] is a prodrug of *morphine* and an inherently less potent μ opioid agonist. Currently available opioids have many differences, such as receptor affinity, pharmacokinetic profiles, available routes of administration, and adverse effect profiles. Some opioids are also available in abuse-
deterrent formulations. Comparing other available opioids to *morphine* is helpful in identifying the unique differences between the agents to guide selection of a safe and effective pain management regimen (Figure 21.5).

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Opioid	Routes of Administration	Comments
Morphine	PO (IR and ER), PR, IM, IV, SC, IA, SL, EA	• **For all drugs listed in this figure: opioid class side effects**. • Hydrophilic properties. • Metabolism through conjugation in liver and P-glycoprotein. • Active metabolites are renally eliminated and accumulate in renal impairment. • Metabolite M3G has no analgesic action, but can be neuroexcitatory. M3G can also cause hyperalgesia. • Metabolite M6G is two to four times more potent than parent drug; accumulation can cause oversedation and respiratory depression. • Abuse-deterrent formulations available.

Methadone	PO, IV, IM, SC	• No active metabolites.
		• Racemic mixture
		  • **Metabolized by many CYP450 isoenzymes:** high risk of drug interactions.
		  • **Substrate of P-glycoprotein.**
		• Long and variable half-life increases risk of overdose.
		• Very lipophilic and redistributes to fat stores.
		• Duration of analgesia is much shorter than elimination half-life. Repeated dosing can lead to accumulation.
		• Can prolong QTc interval and cause torsades de pointes.
		• Warning: Conversion to and from *methadone* and other opioids should be done with great care, since equianalgesic dosing varies dramatically.

Fentanyl	IV, EA, IA, TD, OTFC, SL, Buccal, Nasal, IM, SC	• 100 times more potent than *morphine*. • Greater lipophilicity and CNS penetration as compared with *morphine*. • Less histamine release, sedation, and constipation in comparison with *morphine*. • Metabolized by CYP3A4. • No active metabolites; option for patients with renal dysfunction but should be used with caution. • Can accumulate if continuous infusion in critically ill patients causing hyperalgesia and oversedation.
Oxycodone	PO (IR and CR)	• Active metabolite is noroxycodone. • Metabolized by CYP2D6 and CYP3A4. • Boxed warning: CYP3A4 drug interactions. • Less histamine release and nausea in comparison with *morphine*. • Abuse-deterrent formulation available.
Oxymorphone	PO (IR and ER), PR, IV	• Immediate release has longer duration of action and elimination half-life (8 hours) compared with other immediate-release opioids. • Oral bioavailability increases with food. • Should be administered 1 to 2 hours after eating. • Bioavailability increased with coadministration of alcohol. • Active metabolites are oxymorphone-3-glucuronide and 6-OH-oxymorphone.
Hydromorphone	PO (IR and ER), PR	• Greater lipophilicity and CNS penetration as compared with *morphine*

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Hydromorphone	PO (IR and ER), PR, IV, SC, EA, IA	• Greater lipophilicity and CNS penetration as compared with *morphine*. • Metabolized via glucuronidation to H6G and H3G, which are renally eliminated and can cause CNS side effects when administered in high doses in patients with renal insufficiency. • Abuse-deterrent formulation available.
Hydrocodone	PO (IR and ER)	• Active metabolite is *hydromorphone*. • Metabolized by CYP2D6 and CYP3A4. • Abuse-deterrent formulations available.
Tapentadol	PO (IR and ER)	• Centrally acting analgesic; μ agonist activity along with inhibition of norepinephrine reuptake. • Efficacy in treating nociceptive and neuropathic pain. • Metabolized predominantly by glucuronidation; no CYP450 interactions. • Seizures and serotonin syndrome can occur in predisposed patients.

Tramadol	PO (IR and ER), Topical	• Metabolized by Phase 1 and 2. CYP2D6, CYP2B6, and CYP3A4 involved in metabolism; watch drug interactions.
		• Serotonin syndrome can occur due to drug interactions.
		• CI for treatment of pain in children <12 years old.
		• CI in children <18 years old after removal of tonsils/adenoids.
		• Use is not recommended in 12–18 years old who are obese, have severe lung disease, or have sleep apnea.
		• Use is not recommended in breastfeeding mothers due to adverse reactions in breastfed infants.
		• Warning:
		  • Renal impairment dosing required.
		  • Review dosing recommendations in severe hepatic impairment.

Codeine	PO, SC	• Prodrug: Metabolized by CYP2D6 to the active drug *morphine*. • Rapid metabolizers of CYP2D6 can experience toxicity. • Inhibitors of CYP2D6 prevent conversion of *codeine* to *morphine*, thereby preventing pain control. • Do not use in patients with renal dysfunction. • Use only for mild or moderate pain. • CI in treatment of pain or cough in children <12 years old. • CI in children <18 years old after removal of tonsils/adenoids. • Use is not recommended in 12–18 years old who are obese, have severe lung disease, or have sleep apnea. • Use is not recommended in breastfeeding mothers due to adverse reactions in breastfed infants.

Opioid	Routes of Administration	Comments
Meperidine	PO, IM, IV, SC, EA, IA	• Not recommended as first-line opioid choice. • Active metabolite normeperidine accumulates with renal dysfunction, leading to toxicity. • *Naloxone* does not antagonize the effects of normeperidine; could worsen seizure activity. • Do not use in elderly, patients with renal or hepatic dysfunction, or for chronic pain management.
Buprenorphine	SL, TD, IM, IV, Buccal (transmucosal), Implant	• Long duration of action; very lipophilic. • Incompletely reversed by *naloxone*. • Risk of respiratory depression increased with concomitant use of benzodiazepines or alcohol. • Theoretically lower incidence of respiratory depression, constipation, and hyperalgesia. • Transdermal patch is applied every 7 days. • Abuse-deterrent formulations available.

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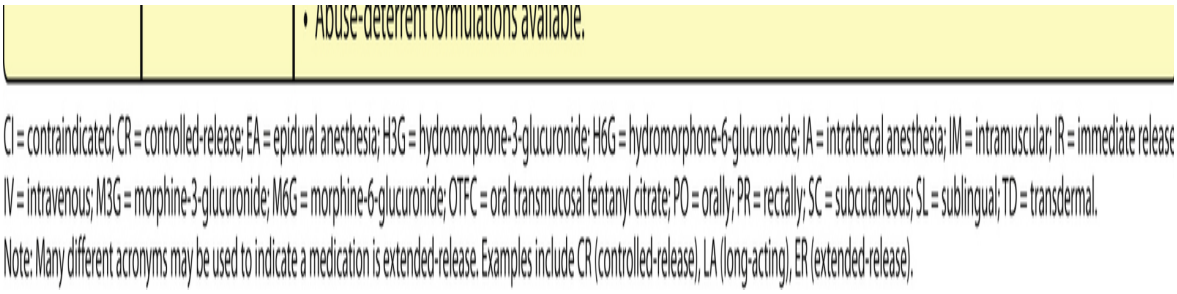

Figure 21.5 Summary of clinically relevant properties for selected opioids.CNS = central nervous system.

A. Morphine

1.Mechanism of action: *Morphine* and other opioids exert analgesic effects by interacting stereospecifically with opioid receptors on the membranes of neuronal cells in the CNS and other anatomic structures, such as the smooth muscles of the gastrointestinal (GI) tract and the urinary bladder. *Morphine* is somewhat selective to the μ opioid receptor but has some affinity for the κ and δ receptors. *Morphine* also inhibits the release of many excitatory transmitters from nerve terminals carrying nociceptive (painful) stimuli. Some therapeutic uses of *morphine* and other opioids are listed in Figure 21.6.

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Therapeutic Use	Comments
Analgesia	*Morphine* is the prototype opioid agonist. Opioids are used for pain in trauma, cancer, and other types of severe pain.
Treatment of diarrhea	Opioids decrease the motility and increase the tone of intestinal circular smooth muscle. [Note: Agents commonly used include *diphenoxylate* and *loperamide* (see Chapter 42).]
Relief of cough	*Morphine* does suppress the cough reflex, but *codeine* and *dextromethorphan* are more commonly used.
Treatment of acute pulmonary edema	Intravenous *morphine* dramatically relieves dyspnea caused by pulmonary edema associated with left ventricular failure, possibly via the vasodilatory effect. This, in effect, decreases cardiac preload and afterload, as well as anxiety experienced by the patient.
Anesthesia	Opioids are used as preanesthetic medications, for systemic and spinal anesthesia, and for postoperative analgesia.

Figure 21.6 Selected clinical uses of opioids.

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2.Actions

a. Analgesia: *Morphine* and other opioids relieve pain by raising the pain threshold at the spinal cord level and by altering the brain's perception of pain. The maximum analgesic efficacy for representative opioid agonists is shown in Figure 21.7.

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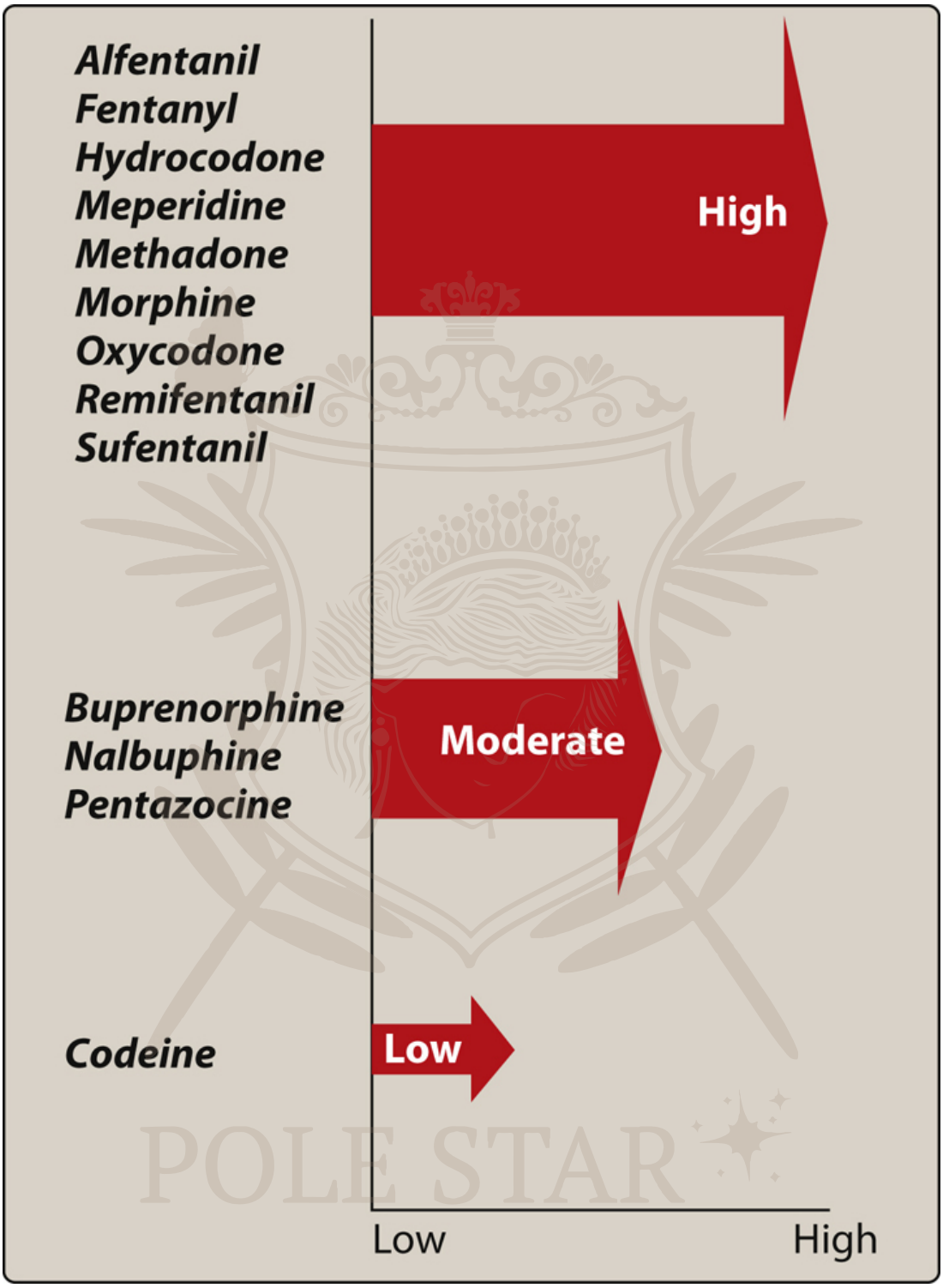

Figure 21.7 A comparison of opioid agonist efficacy.

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b. Euphoria: *Morphine* produces a powerful sense of contentment and well-being. Euphoria may be caused by disinhibition of the dopamine-containing neurons of the ventral tegmental area, leading to increased dopamine in the nucleus accumbens and producing positive reinforcement.

c. Respiration: Proper function of the ventilatory control system is necessary for appropriate uptake of oxygen and removal of carbon dioxide (CO_2). *Morphine* causes respiratory depression by reduction of the responsiveness of medullary respiratory center neurons to carbon dioxide. This can occur with ordinary doses of *morphine* in patients who are opioid naïve and can be accentuated as the dose is increased, until ultimately respiration ceases. Respiratory depression is the most common cause of death in acute opioid overdoses. Tolerance to this effect develops with repeated dosing, which allows for the safer use of *morphine* for the treatment of pain when the dose is correctly titrated.

d. Depression of cough reflex: Both *morphine* and *codeine* have antitussive properties and cause cough suppression by direct depression of the medullary cough reflex. In general, cough suppression does not correlate closely with analgesic and respiratory depressant properties of opioid drugs. The receptors involved in the antitussive action appear to be different from those involved in analgesia.

e. Miosis: The pinpoint pupil (Figure 21.8) characteristic of *morphine* use results from stimulation of μ and κ receptors. There is little tolerance to this effect. [Note: This is important diagnostically because many other causes of coma and respiratory depression produce dilation of the pupil.]

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Figure 21.8 Characteristic pinpoint pupil associated with *morphine* use.

f. Emesis: *Morphine* directly stimulates the chemoreceptor trigger zone in the area postrema. The area postrema is located on the dorsal surface of the medulla oblongata and is part of the brainstem. Stimulation of this area causes vomiting.

g. GI tract: *Morphine* relieves diarrhea by decreasing the motility and increasing the tone of the intestinal circular smooth muscle. *Morphine* also increases the tone of the anal sphincter. *Morphine* and other opioids produce constipation, with little tolerance developing to this effect. *Morphine* can also increase

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biliary tract pressure due to contraction of the gallbladder and constriction of the biliary sphincter.

h. Urinary tract: *Morphine* has been shown to inhibit the urinary bladder voiding reflex and increase sphincter tone resulting in urinary retention. Postoperative urinary retention is commonly seen with *morphine* following intravenous or epidural administration. Oral administration can also lead to urinary retention. Some patients might require catheterization.

i. Cardiovascular: *Morphine* has no major effects on blood pressure or heart rate at lower dosages, but hypotension and bradycardia may occur at higher doses. Because of respiratory depression and carbon dioxide retention, cerebral vessels dilate and increase cerebrospinal fluid pressure. *Morphine* is usually contraindicated in individuals with head trauma or severe brain injury.

j. Histamine release: *Morphine* releases histamine from mast cells causing urticaria, sweating, bronchoconstriction, and vasodilation (hypotension). It should be used with caution in patients with asthma, as it can precipitate or exacerbate an asthmatic attack. Agents such as *fentanyl*, which have a lower incidence of histamine release, may be better options in this case.

k. Hormonal actions: Prolonged use of *morphine* may lead to opioid-induced androgen deficiency due to suppression of the hypothalamic–pituitary–gonadal axis. This results in decreased production of sex hormones, especially testosterone, resulting in many clinical symptoms (Figure 21.9).

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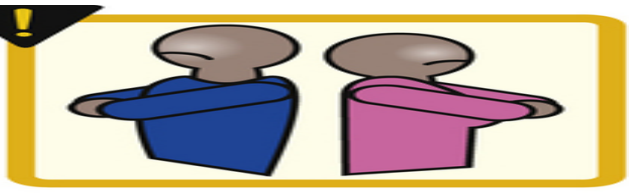
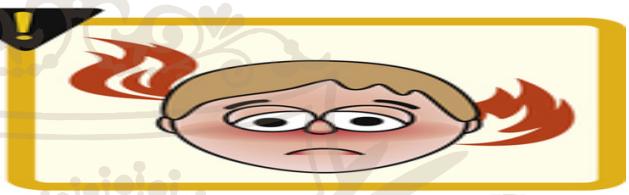
Sexual dysfunction



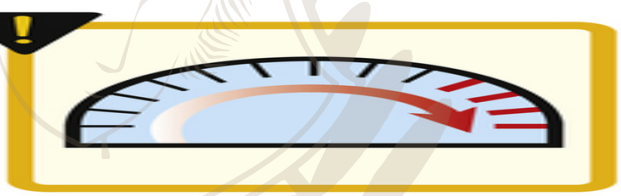
Fatigue

Hot flashes



Depression

Weight gain



Decreased muscle mass

Osteoporosis

Possible infertility

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Figure 21.9 Clinical symptoms associated with opioid-induced androgen deficiency (OPIAD).

l. Labor: *Morphine* may prolong the second stage of labor by transiently decreasing the strength, duration, and frequency of uterine contractions.

3.Pharmacokinetics

a. Administration: *Morphine* has a linear pharmacokinetic profile; however, absorption of *morphine* after oral administration is slow and erratic. Extended-release oral preparations provide more consistent plasma levels. Because significant first-pass metabolism of *morphine* occurs in the liver, subcutaneous and intravenous (IV) injections produce the most reliable response.

b. Distribution: *Morphine* rapidly enters all body tissues, including the fetus of pregnant women. [Note: It should not be used for analgesia during labor. Infants born to mothers with opioid use disorder can experience neonatal abstinence syndrome, showing physical dependence on opioids and exhibiting withdrawal symptoms if opioids are not administered]. Only a small percentage of *morphine* crosses the blood–brain barrier, because *morphine* is the least lipophilic of the common opioids. By contrast, the more lipid-soluble opioids, such as *fentanyl* and *methadone*, readily penetrate the CNS.

c. Metabolism and elimination: *Morphine* is conjugated with glucuronic acid in the liver to two active metabolites (morphine-6-glucuronide [M6G] and morphine-3-glucuronide [M3G]), which are renally excreted. M6G is a potent analgesic. M3G does not have analgesic activity but is believed to cause neuroexcitatory and antianalgesic effects. The duration of action of *morphine* is 4 to 5 hours when administered systemically to opioid-naïve individuals but considerably longer when injected epidurally because its low lipophilicity prevents redistribution from the epidural space.

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4.Adverse effects: Many adverse effects are common across the entire opioid class (Figure 21.10). With most μ agonists, severe respiratory depression can occur and may result in death from acute opioid overdose. Respiratory drive may be suppressed in patients with respiratory disorders such as obstructive sleep apnea, chronic obstructive pulmonary disease, or cor pulmonale, so close monitoring is necessary when using opioids. Opioid-induced constipation (OIC) is a common adverse effect. Initial management includes a nonprescription stimulant laxative such as *senna.* Peripherally acting μ-opioid receptor antagonists such as *methylnaltrexone*, *naloxegol*, and *naldemedine* are prescription drugs available for the treatment of laxative refractory OIC. [Note: *Lubiprostone* is a chloride channel activator that is indicated for OIC and irritable bowel syndrome; see Chapter 42.] *Morphine* should be used with caution in patients with liver disease and renal dysfunction.

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Hypotension

Dysphoria (anxiety, depression, or unease)

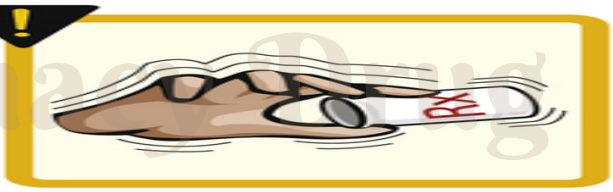
Sedation

Constipation

Urinary retention

Nausea

Potential for addiction



Respiratory depression

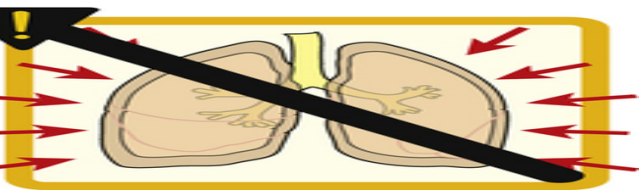


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Figure 21.10 Adverse effects commonly observed in individuals treated with opioids.

5.Tolerance and dependence: Repeated use produces tolerance to the respiratory depressant, analgesic, euphoric, emetic, urinary retention, and sedative effects of *morphine.* Tolerance to miosis (constriction of the pupils) or constipation usually does not develop. Physical and psychological dependence can occur with *morphine* and other agonists. Abrupt discontinuation can produce a series of autonomic, motor, and psychological responses that can be severe, and can prove detrimental in patients with severe comorbid conditions, although it is rare that withdrawal effects cause death.

6.Drug interactions: Drug interactions with *morphine* are possible. The depressant actions of *morphine* are enhanced by coadministration with CNS depressant medications such as phenothiazines, monoamine oxidase inhibitors (MAOIs), and benzodiazepines. Guidelines for opioid prescribing recommend clinicians avoid simultaneous prescribing of opioids and benzodiazepines. A boxed warning also has been included on the labeling of both opioids and benzodiazepines to alert prescribers of this dangerous combination. Additionally, serious breathing difficulties have also been noted with the coadministration of opioids and gabapentinoids (for example, *gabapentin* and *pregabalin*).

B. Codeine

Codeine [KOE-deen] is a naturally occurring opioid and a weak analgesic compared with *morphine.* It is used for mild to moderate pain. The analgesic actions of *codeine* are derived from its conversion to *morphine* by CYP2D6 (see Chapter 1). CYP2D6 activity varies among patients, and ultrarapid metabolizers may experience higher levels of *morphine*, leading to increased risk of overdose and toxicity (see Chapter 48). Life-threatening respiratory depression and death have occurred in children who received *codeine*, mostly following tonsillectomy and/or adenoidectomy, which led to its boxed warning for use in this patient population. *Codeine* is commonly used in

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combination with *acetaminophen* for management of pain. The drug exhibits good antitussive activity at doses that do not cause analgesia. *Dextromethorphan* [dex-troe-meth-OR-fan] is a synthetic cough depressant that has relatively no analgesic action and much lower potential for abuse in usual antitussive doses. It is preferred over *codeine* in most situations where cough suppression is needed.

C. Oxycodone and oxymorphone

Oxymorphone [ox-ee-MOR-fone] and *oxycodone* [ok-see-KOE-done] are semisynthetic analogs of *morphine* and *codeine*, respectively. When administered orally, the potency of *oxymorphone* is approximately three times that of *morphine. Oxymorphone* is available in both immediate-release and extended-release oral formulations. This agent has no clinically relevant drug interactions associated with the CYP450 enzyme system. *Oxycodone* is approximately two times more potent than *morphine* and is available in an immediate-release formulation, alone or in combination with *acetaminophen*, *aspirin*, *or ibuprofen.* An extended-release formulation is also available. *Oxycodone* is mainly metabolized via the CYP2D6 (to *oxymorphone*) and CYP3A4 enzymes and is susceptible to drug–drug interactions.

D. Hydromorphone and hydrocodone

Hydromorphone [hye-droe-MORE-fone] and *hydrocodone* [hye-droe-KOE-done] are semisynthetic analogs of *morphine* and *codeine*, respectively. Oral *hydromorphone* is approximately 4 to 7 times more potent than oral *morphine.* It is preferred over *morphine* in patients with renal dysfunction due to less accumulation of active metabolites. *Hydrocodone* is the methyl ether derivative of *hydromorphone* but is a weaker analgesic than *hydromorphone*, with oral analgesic efficacy comparable with that of *morphine.* This agent is often combined with *acetaminophen* or *ibuprofen* to treat moderate to severe pain. It is also used as an antitussive. *Hydrocodone* is metabolized in the liver to several metabolites, one of which is *hydromorphone* via the actions of CYP2D6. Therefore, *hydrocodone* is susceptible to drug interactions with strong inhibitors or inducers of CYP2D6.

E. Fentanyl

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Fentanyl [FEN-ta-nil] is a synthetic opioid chemically related to *meperidine. Fentanyl* has approximately 80- to100-fold the analgesic potency of *morphine* and is used for anesthesia and acute pain management. The drug is highly lipophilic and has a rapid onset and short duration of action (15-30 minutes). It is usually administered IV, epidurally, or intrathecally. [Note: Rapid IV infusion of *fentanyl* and related compounds may result in skeletal muscle and chest wall rigidity, impaired ventilation, or respiratory distress. This is more commonly seen in pediatric patients.] *Fentanyl* is combined with local anesthetics to provide epidural analgesia for labor and postoperative pain. IV *fentanyl* is used in anesthesia for its analgesic and sedative effects. Many fast-acting transmucosal and nasal *fentanyl* products are available for cancer-related breakthrough pain in opioid-tolerant patients. The transdermal patch creates a reservoir of the drug in the skin and has a delayed onset of at least 12 hours and a prolonged offset. The patch is used for management of chronic severe pain. It is contraindicated in opioid-naïve patients and should not be used in management of acute or postoperative pain. *Fentanyl* is metabolized to inactive metabolites by CYP3A4, and drugs that inhibit this isoenzyme can potentiate the effect of *fentanyl*.

Clinical Application 21.1: Opioids and the Cytochrome P450 Enzyme System

When selecting the optimal opioid for a patient, the risk of drug interactions must be considered. Opioids that rely on the CYP450 enzyme system for metabolism have a higher risk of drug interactions than agents that do not. Opioids that do not predominantly rely on the CYP450 enzyme system for metabolism include *morphine, oxymorphone, hydromorphone,* and *tapentadol.* Therefore, these agents have a lower risk of drug interactions.

F. Sufentanil, alfentanil, remifentanil, and carfentanil

Sufentanil [soo-FEN-ta-nil], *alfentanil* [al-FEN-ta-nil], *remifentanil* [rem-ih-FEN-ta-nil], and *carfentanil* [car-FEN-ta-nil] are synthetic opioid agonists related to *fentanyl.* These agents differ in potency and metabolic disposition. *Sufentanil* and *carfentanil* are even more potent than *fentanyl*, whereas the other two are less potent and shorter acting. Intravenous *sufentanil*, *alfentanil*, and *remifentanil* are mainly

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used for their analgesic and sedative properties during surgical procedures requiring anesthesia. *Sufentanil* is also available as a sublingual tablet for management of severe acute pain in the perioperative setting. This agent must be administered in a medically supervised setting and is not for use at home. *Carfentanil* is approximately 100 times more potent than *fentanyl* (10,000 times more potent than *morphine*). The drug is only approved for veterinary use and is not used in clinical practice; however, it is of toxicological interest as it is used to contaminate *heroin* and has contributed to several opioid-related deaths.

G. Methadone

Methadone [METH-a-done] is a synthetic opioid that has variable equianalgesic potency compared with that of *morphine*, and the conversion between the two products is not linear. *Methadone* is a μ agonist, an antagonist of the *N*-methyl-d-aspartate (NMDA) receptor, and a norepinephrine and serotonin reuptake inhibitor. Therefore, it is useful in the treatment of both nociceptive and neuropathic pain. *Methadone* may also be used for opioid withdrawal and maintenance therapy in the setting of prescription opioid or *heroin* substance use disorder. The withdrawal syndrome with *methadone* is milder but more protracted (days to weeks) than that with other opioids. *Methadone* induces less euphoria and has a longer duration of action than *morphine*.

Clinical Application 21.2: Methadone Dosing Based on Indication

Methadone is a very complex and effective opioid that can be used for moderate-to-severe around-the-clock pain that is nociceptive and neuropathic in origin. Only the 5- or 10-mg tablets are approved for pain management; they are available for purchase with a prescription at local pharmacies. *Methadone* is also used for the maintenance of opioid use disorder in a federally certified opioid treatment program. For this indication, patients are treated with 40-mg tablets or a liquid solution. It is important for clinicians to understand the differences in dosing for each indication for legal purposes, as well as the complex pharmacokinetics, potential cardiac effects, and numerous drug interactions when prescribing this medication.

1.Pharmacokinetics: Understanding the pharmacokinetics of *methadone* is important to ensure proper use. Compared with

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morphine, *methadone* is better absorbed after oral administration (bioavailability of *methadone* 36%-100%; *morphine* 20%-40%) After oral administration, *methadone* is biotransformed in the liver and excreted almost exclusively in the feces. *Methadone* is lipophilic, rapidly distributes throughout the body, and releases slowly during redistribution and elimination. This translates into a long half-life ranging from 12 to 40 hours, although it may extend up to 150 hours. Despite the extended half-life, the actual duration of analgesia ranges from 4 to 8 hours. Attainment of steady state can vary dramatically, ranging from 35 hours to 2 weeks, so dosage adjustments should occur only every 5 to 7 days. Upon repeated dosing, *methadone* can accumulate due to the long terminal half-life, leading to toxicity. Overdose is possible when prescribers are unaware of the long half-life, the incomplete cross-tolerance between *methadone* and other opioids, and the titration guidelines to avoid toxic accumulation. The metabolism is variable due to involvement of multiple CYP450 isoenzymes, some of which are affected by known genetic polymorphisms. As such, *methadone* is susceptible to many drug–drug interactions.

Clinical Application 21.3: Cross-Tolerance of Opioids

Patients treated with opioid medications may have intolerance to a particular opioid and experience adverse effects such as itching, nausea, or headache. Repeated administration of the opioid can result in the development of tolerance to the specific adverse effect in most situations. Patients can also develop tolerance to the analgesic effects of the opioid, resulting in a gradual loss of efficacy. Rotating from one opioid to another after chronic exposure can result in “cross-tolerance,” leading to decreased analgesia, especially if acting on the same receptor site. However, switching opioids more often results in “incomplete cross-tolerance,” where the newly substituted opioid binds to different receptor subtypes due to patient variability and pharmacogenomics. This results in greater potency at the receptor, greater pain relief, and also an increased risk for adverse effects. The American Pain Society guidelines recommend a dosage reduction of 25% to 50% when converting between opioids for chronic pain management, but an exact percentage reduction has not been established. Patients with poorly controlled pain often do not require as significant of a reduction in dose when rotating to another opioid.

2.Adverse effects: *Methadone* can produce physical dependence like that of *morphine*, but it has less neurotoxicity than

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morphine due to lack of active metabolites. *Methadone* is also constipating, but less so than *morphine. Methadone* can prolong the QT_c interval and cause torsades de pointes, possibly by interacting with cardiac potassium channels. Baseline and routine ECG monitoring is recommended.

H. Meperidine

Meperidine [me-PER-i-deen] is a lower-potency synthetic opioid structurally unrelated to *morphine.* It is used for acute pain and acts primarily as a κ agonist, with some μ agonist activity. *Meperidine* is very lipophilic and has anticholinergic effects, resulting in an increased incidence of delirium compared with other opioids. It does not typically cause miosis (potentially due to its anticholinergic properties). *Meperidine* has an active metabolite (normeperidine), which is potentially neurotoxic. Normeperidine is renally excreted, and in patients with renal insufficiency, accumulation of the metabolite may lead to delirium, hyperreflexia, myoclonus, and seizures. Due to the short duration of action and the potential for toxicity, *meperidine* should only be used for short-term (≤48 hours) management of pain. *Meperidine* should not be used in elderly patients or those with renal insufficiency, hepatic insufficiency, preexisting respiratory compromise, or concomitant or recent administration of MAOIs (for example, *phenelzine*, *selegiline*, *isocarboxazid*). Serotonin syndrome has been reported in patients receiving both *meperidine* and selective serotonin reuptake inhibitors (SSRIs).

IV. PARTIAL AGONISTS AND MIXED AGONIST–ANTAGONISTS

Partial agonists bind to the opioid receptor, but they have less intrinsic activity than full agonists (see Chapter 2). There is a ceiling to the pharmacologic effects of these agents. Drugs that stimulate one receptor but block another are termed mixed agonist–antagonists. The effects of these drugs depend on previous exposure to opioids. In individuals who are opioid naïve, mixed agonist–antagonists show agonist activity and are used to relieve pain. In the presence of a full agonist, the agonist–

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antagonist drugs and partial agonists may precipitate opioid withdrawal symptoms, displacing the full agonist from the receptor.

A. Buprenorphine

Buprenorphine [byoo-pre-NOR-feen] acts as a partial agonist at the μ receptor and the ORL-1 receptor, and an antagonist at the κ and δ receptors. Despite the partial agonist activity at the μ receptor, it has potent receptor affinity and provides analgesia similar to full mu opioid receptor agonists. *Buprenorphine* has an analgesic potency 25 to 100 times that of *morphine*, depending on the formulation and route. However, its risk of toxicity is much lower compared with that of full μ opioid agonists. *Buprenorphine* is very lipophilic and has a longer duration of action due to its high affinity for the opioid receptors when compared with *morphine.* Due to high affinity for the μ receptor, *buprenorphine* can displace full μ agonists, leading to withdrawal symptoms in patients currently taking opioids. Because of the partial μ agonist activity, *buprenorphine* provides a "ceiling effect," causing less euphoric effects and a lower abuse potential than that of full agonists. Additionally, the risk of opioid-induced respiratory depression may be lower when compared with full agonists, except when combined with CNS depressants such as benzodiazepines and alcohol. *Buprenorphine* is available in several formulations. Transdermal, buccal, and injectable formulations are indicated for the relief of moderate to severe pain. Sublingual tablet or film, buccal film, an extended-release injection, and the subdermal implant are used in the management of opioid use disorder. In contrast to *methadone*, which is available only at specialized clinics when used for opioid detoxification or maintenance, *buprenorphine* is approved for office-based treatment of opioid use disorder. It has been shown to have shorter and less severe withdrawal symptoms compared with *methadone,* although data have shown *methadone* to have greater patient retention rates (Figure 21.11).

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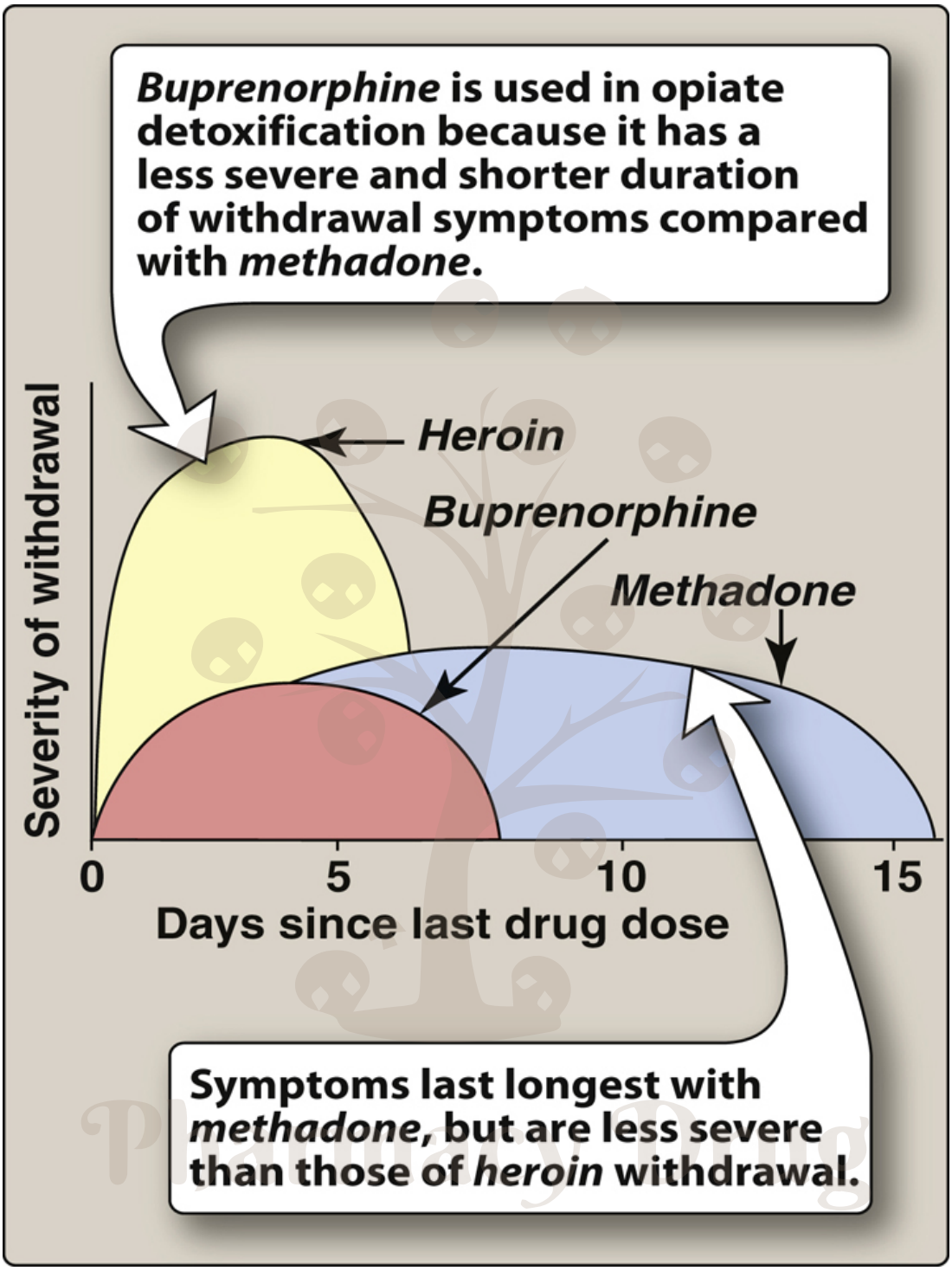

Figure 21.11 Severity of opioid withdrawal symptoms after abrupt withdrawal of equivalent doses of *heroin*, *buprenorphine*, and *methadone*.Modified from N. L.Benowitz . Pharmacologic aspects of cigarette smoking and nicotine addiction. *N. Engl. J. Med*. 319: 1318 (1988).

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Adverse effects include respiratory depression, which cannot easily be reversed by *naloxone,* and decreased (or, rarely, increased) blood pressure, nausea, constipation, and dizziness. Additionally, *buprenorphine* has been associated with prolongation of the QTc interval. Although the clinical significance is controversial, it is still recommended to monitor patients on concomitant agents that may prolong the QTc interval or patients with preexisting heart abnormalities. *Buprenorphine* is metabolized via the CYP3A4 enzyme system, and caution should be used when the drug is coadministered with strong CYP3A4 inhibitors.

B. Pentazocine

Pentazocine [pen-TAZ-oh-seen] acts as a full agonist at the κ receptors and is a partial agonist at μ receptors. It can be administered parenterally or as an oral agent, which is only available in combination with *naloxone. Pentazocine* produces less euphoria compared with *morphine*, but in higher doses, respiratory depression, increased blood pressure, tachycardia, and hallucinations can occur. For these reasons, *pentazocine* is rarely used for management of pain. Despite its weakly antagonist action on full μ agonists, *pentazocine* does not antagonize the respiratory depression of *morphine*, but it can precipitate withdrawal effects in a *morphine* user. *Pentazocine* should be used with caution in patients with angina or coronary artery disease since it can increase blood pressure.

C. Nalbuphine and butorphanol

Nalbuphine [NAL-byoo-feen] and *butorphanol* [byoo-TOR-fa-nole] are mixed opioid agonist–antagonists. Like *pentazocine*, they play a limited role in the treatment of chronic pain. *Butorphanol* is available in a nasal spray that has been used for severe headaches, but it has been associated with misuse. Accidental exposure of the intranasal formulation can result in a fatal overdose, especially in children. Both products are available in an injectable formulation. Their propensity to cause psychotomimetic effects is less than that of *pentazocine.* In contrast to *pentazocine* and *butorphanol*, *nalbuphine* does not affect the heart or increase blood pressure. A benefit of all three medications is that they exhibit a ceiling effect for respiratory depression.

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V. OTHER ANALGESICS

A. Tapentadol

Tapentadol [ta-PEN-ta-dol]is a full μ opioid receptor agonist and a norepinephrine reuptake inhibitor. It is approximately 2 to 3 times less potent than oral *morphine* and has better gastrointestinal tolerability compared with *oxycodone. Tapentadol* is used to manage moderate to severe acute and chronic pain, including neuropathic pain associated with diabetic peripheral neuropathy. It is mainly metabolized to inactive metabolites via glucuronidation and does not inhibit or induce the CYP450 enzyme system. Because *tapentadol* does not produce active metabolites, dosing adjustment is not necessary in mild to moderate renal impairment. *Tapentadol* should be avoided in patients who have received MAOIs within the past 14 days and used with caution in patients taking serotoninergic drugs due to a higher risk of serotonin syndrome. It is available in an immediate-release and extended-release formulation.

B. Tramadol

Tramadol [TRA-ma-dole] is a centrally acting analgesic that binds weakly to the μ opioid receptor and weakly inhibits reuptake of norepinephrine and serotonin. It undergoes extensive metabolism via CYP2D6, leading to an active metabolite, which has a much higher affinity for the μ receptor than the parent compound. *Tramadol* is also metabolized by CYP3A4 and CYP2B6. It is used to manage mild to moderate pain. Of note, *tramadol* has less respiratory-depressant activity compared with *morphine.* Administration of *naloxone* can only partially reverse *tramadol* toxicity and has been associated with an increased risk of seizures. Rare but serious adverse effects include anaphylactoid reactions and serotonin syndrome. The risk of serotonin syndrome is increased when *tramadol* is administered in combination with other serotonergic agents or when its plasma concentrations are increased due to a drug interaction. Overdose or drug–drug interactions with SSRIs, MAOIs, and TCAs can lead to toxicity manifested by CNS excitation and seizures. *Tramadol* should be used with caution in patients with a history of seizures. As with other agents

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that bind the μ opioid receptor, *tramadol* has been associated with misuse and substance use disorder.

C. Oliceridine

Oliceridine [OH-li-SER-I-deen] is a novel synthetic, centrally and peripherally acting μ-opioid agonist that preferentially binds to the G protein–coupled pathway with reduced β-arrestin post-receptor recruitment. Activation of β-arrestin contributes to respiratory depression and gastrointestinal dysfunction. Therefore, reducing activation of β-arrestin has the potential to reduce these effects, as compared with traditional opioids like *morphine. Oliceridine* is only available in an IV formulation and is indicated for moderate-to-severe acute pain. It possesses a more rapid onset and shorter duration and half-life and is relatively five times as potent as compared with IV *morphine.* Respiratory depression may still occur with this agent. Other adverse effects include dizziness, headache, nausea, vomiting, and constipation. *Oliceridine* undergoes significant metabolism via CYP2D6 and CYP3A4 and has no known active metabolites. In patients with mild to moderate hepatic impairment, the dosing intervals should be extended. In severe hepatic disease, the initial dose should be reduced, and subsequent doses administered only after assessment of the clinical status. Dosage adjustments are not necessary for renal impairment.

VI. ANTAGONISTS

The opioid antagonists bind with high affinity to opioid receptors, but they fail to activate the receptor-mediated response. Administration of opioid antagonists produces no profound effects in individuals not taking opioids. In opioid-dependent patients, antagonists rapidly reverse the effect of agonists, such as *morphine* or any full μ agonist, and precipitate the symptoms of opioid withdrawal. Figure 21.12 summarizes some signs and symptoms of opioid withdrawal.

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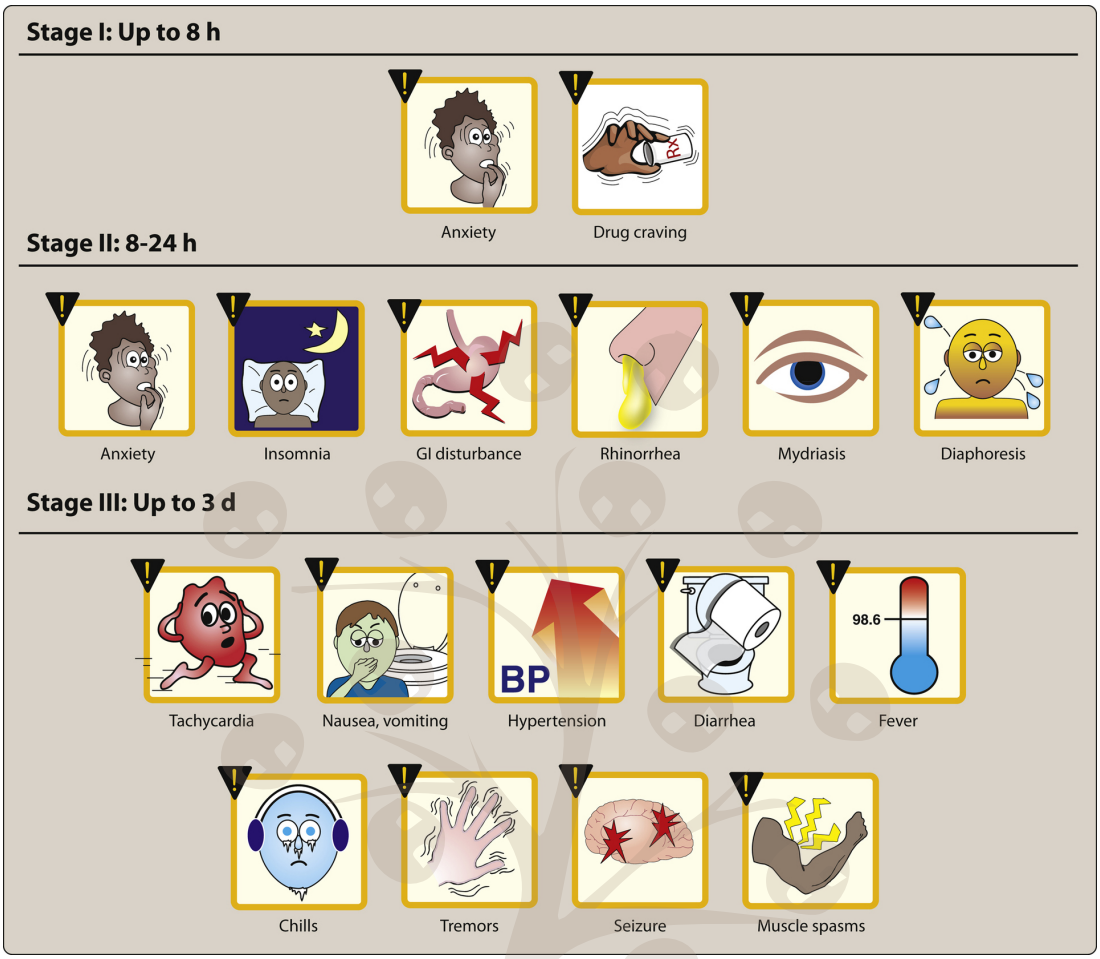

Figure 21.12 Opiate withdrawal syndrome.GI = gastrointestinal.

A. Naloxone

Naloxone [nal-OX-own] is a competitive antagonist at μ, κ, and δ receptors, with a 10-fold higher affinity for μ than for κ receptors. It rapidly displaces all receptor-bound opioid molecules and, therefore, can reverse the effects of *morphine* overdose, such as respiratory depression and coma within 2 minutes of IV administration. *Naloxone* can also be administered intramuscularly, subcutaneously, and intranasally, with a slightly longer onset of action; however, little to no clinical effect is seen with oral *naloxone* due to extensive first-pass metabolism. Since *naloxone* has a half-life of 30 to 90 minutes, a patient who has been treated for an overdose and recovered may lapse back into respiratory depression, depending on the opioid ingested and dosage form of that opioid. [Note: Much higher doses

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and continuous administration of *naloxone* are needed to reverse the effects of *buprenorphine* due to its high affinity for the μ receptor. This strategy may also be needed for highly potent opioids.]

Naloxone is available in an autoinjector and a nasal inhaler for community distribution for treatment of opioid overdose involving *heroin* or prescription opioids. It is imperative that prescribers counsel the patient and family members regarding the availability of these products, proper instructions for use, and the importance of calling emergency services in the case of overdose. In the United States, current laws allow patients to purchase *naloxone* from community pharmacies without a prescription.

B. Naltrexone

Naltrexone [nal-TREX-own] has actions similar to those of *naloxone*, but it has a longer duration of action and can be given orally. For example, a single oral dose of *naltrexone* blocks the effect of injected *heroin* for up to 24 hours, and the intramuscular formulation blocks the effect for 30 days. *Naltrexone* is approved for the management of opioid use disorder and alcohol use disorder. It is used for rapid opioid detoxification in combination with *clonidine* (and, sometimes, with *buprenorphine*). *Naltrexone* has been associated with elevated liver enzymes, and monitoring of hepatic function is recommended. Common side effects include nausea and vivid dreams or nightmares. To decrease the risk of nightmares, patients should be instructed to take the medication in the morning, rather than the evening.

Chapter Summary

- Pain is a complex experience that is influenced by varying degrees of biological, psychological, and social factors. When crafting a therapeutic regimen, the clinician needs to perform a thorough and complete assessment of pain.
- Opioids are divided into clinical classes based on chemical structure. All opioids have major effects mediated by the three main receptor families commonly designated as μ (mu, MOP), κ (kappa, KOP), and δ (delta, DOP).
- *Morphine* is the prototypical μ receptor agonist. Comparing other available opioids to *morphine* is helpful in identifying the unique differences in side effect profiles and relevant potencies to guide the selection of a safe and effective pain management regimen.

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- Although all opioids have similar side effects, it is important to consider the differences in metabolism, mechanism of action, and elimination when designing a therapeutic regimen for an individual patient.
- *Methadone* is a very complex and effective opioid that can be used for moderate-to-severe around-the-clock pain that is nociceptive and neuropathic in origin. Due to the complex pharmacokinetic properties, cardiac effects, and numerous drug interactions, this opioid should be used with caution.
- *Buprenorphine* serves as a treatment option for patients at risk for respiratory depression (for example, obesity, respiratory conditions, concomitant CNS depressants) or those experiencing hyperalgesia with the current opioid regimen. Established conversions across different formulations are relatively lacking to date.
- *Naloxone* is a competitive antagonist at the μ, κ, and δ receptors and can reverse the effects of most opioid-induced respiratory depression. It is available for community distribution and should be made available to patients who have opioids present in their household.

STUDY QUESTIONS

Choose the ONE best answer.

21.1 Which of the following agents listed is a phenanthrene opioid that exhibits a full and immediate response to treatment with naloxone in the case of overdose?

A. Meperidine
B. Fentanyl
C. Buprenorphine
D. Morphine

Correct answer = D. Morphine is a phenanthrene. A morphine overdose can be effectively treated with naloxone. Naloxone antagonizes the opioid by displacing it from the receptor, but there are cases in which naloxone is not effective. Naloxone is effective for fentanyl overdoses; however, fentanyl is a phenylpiperidine, and not a phenanthrene. Meperidine is a phenylpiperidine, not a phenanthrene, and the active metabolite, normeperidine, is not reversible by naloxone. The effects of buprenorphine are only partially reversible by naloxone. In most cases of buprenorphine overdose, the dose of naloxone needs to be high and continuous due to the higher binding affinity to the mu receptor.

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21.2 Which of the following statements is correct regarding morphine?

A. Morphine is the most lipophilic opioid.
B. Morphine is metabolized through CYP2D6 and CYP3A4 and has numerous drug interactions.
C. Morphine has active metabolites that can accumulate in renal impairment, leading to clinically relevant effects.
D. Morphine can cause opioid-induced constipation upon initiation of opioid therapy, but tolerance occurs after 1 to 2 weeks of opioid exposure.

Correct answer = C. Morphine has two active metabolites M3G and M6G, which are renally eliminated. When these active metabolites accumulate, clinically relevant effects can occur; see Figure 21.5 for more details. Morphine is hydrophilic and is metabolized through conjugation in the liver. Morphine does not rely on the CYP450 enzyme system for metabolism, and this decreases the risk of drug interactions. Morphine can cause opioid-induced constipation upon initiation of opioid therapy, but tolerance to opioid-induced constipation does not occur.

21.3 A 76-year-old woman presents to the pain clinic with severe pain secondary to a compression fracture in the lumbar spine. Her past medical history is significant for renal insufficiency. She reports that the pain has been uncontrolled with acetaminophen. Which of the following is the best opioid for this patient?

A. Morphine (oral)
B. Fentanyl (transdermal patch)
C. Meperidine (oral)
D. Hydrocodone/acetaminophen (oral)

Correct answer = D. Hydrocodone/acetaminophen is the best choice. It is very important to use a low dose and monitor closely for proper pain control and adverse effects. Morphine is not the best choice due to the active metabolites that can accumulate in renal insufficiency. The transdermal patch is not a good option, since her pain is considered acute and she is opioid naïve. Meperidine should not be used for chronic pain, nor should it be used in a patient with renal insufficiency.

21.4 A 56-year-old patient has suffered with painful diabetic neuropathy and severe chronic back pain with radiculopathy

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secondary to spinal stenosis for many years. The patient has failed to receive relief from neuropathic pain with first-line agents such as tricyclics, SNRIs, or anticonvulsants. Which of the following opioid has a dual mechanism of action and should be considered to treat both nociceptive and neuropathic pain in this patient?

A. Tapentadol
B. Oxymorphone
C. Morphine
D. Hydrocodone

Correct answer = A. Tapentadol has a unique mechanism of action in comparison with the other choices listed. Tapentadol has a dual mechanism of action (μ agonist and norepinephrine reuptake inhibition), which has been shown to effectively treat neuropathic pain associated with diabetic peripheral neuropathy. All other μ agonists listed might have some efficacy in treating neuropathic pain, but they do not have the dual mechanism like tapentadol.

21.5 Which of the following statements regarding methadone is correct?

A. Methadone is an excellent choice for analgesia in most patients because there are limited drug–drug interactions.
B. The duration of analgesia for methadone is much shorter than the elimination half-life.
C. The equianalgesic potency of methadone is similar to that of morphine.
D. The active metabolites of methadone accumulate in patients with renal dysfunction.

Correct answer = B. The duration of analgesia with methadone is much shorter than the elimination half-life, leading to dangers of accumulation and increased potential for respiratory depression and death. The equianalgesic potency of methadone is extremely variable based on many factors, and only providers familiar with methadone should prescribe this agent. The drug interactions associated with methadone are numerous due to the multiple liver enzymes involved in metabolism of the drug. Methadone does not have active metabolites, which makes it a treatment option in patients with renal dysfunction.

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21.6 A 57-year-old man has been treated with extended-release tapentadol for chronic nonmalignant pain for 2 years. He now reports increased pain in the afternoon while at work. Which of the following is a short-acting opioid and is the best choice for this patient's breakthrough pain?

A. Hydrocodone
B. Methadone
C. Buprenorphine
D. Nalbuphine

Correct answer = A. Hydrocodone is a commonly used short-acting agent that is commercially available in combination with either acetaminophen or ibuprofen. Methadone should not routinely be used for breakthrough pain due to the unique pharmacokinetics and should be reserved for practitioners who have experience with this agent and understand the variables associated with this drug. Buprenorphine and nalbuphine could precipitate withdrawal in patients who are currently taking a dual mechanism opioid such as tapentadol.

21.7 A 64-year-old man is hospitalized following a car accident in which he sustained a broken leg and arm. He has been converted to oral morphine in anticipation of discharge from the hospital. Upon discharge, which of the following medications should he receive along with the morphine?

A. Docusate sodium
B. Senna
C. Methylphenidate
D. Diphenhydramine

Correct answer = B. A bowel regimen should be prescribed with the initiation of the opioid since constipation is very common and can occur at any time. Tolerance to this adverse effect does not occur. Senna is a stimulant laxative that is available over the counter. Docusate sodium is a stool softener that is ineffective in opioid-induced constipation when used as a single agent. Combination products that include both docusate and senna are commonly used and can be effective, mainly due to the actions of senna. Diphenhydramine can be used for urticaria that might occur with the initiation of an opioid. Methylphenidate has been used for opioid-induced sedation in certain situations, but these issues are not reported in this case.

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21.8 A 67-year-old man is treated with hydrocodone/acetaminophen for chronic nonmalignant pain with no changes in dosage for 2 years. His pain has been fairly well controlled, and he remains active, reports satisfaction with his pain regimen, and denies any side effects. He has been recently diagnosed with COPD and obstructive sleep apnea. Which of the following is the best treatment recommendation for him at this time?

A. Taper off all opioids immediately due to increased risk of opioid-induced respiratory depression.
B. Prescribe oral naloxone tablets to have at home in case he experiences an opioid overdose.
C. Prescribe naloxone nasal spray to have at home and counsel patient and family members on proper use in case an opioid overdose occurs.
D. No action is needed at this time. His pain is well controlled, and he is reporting no side effects.

Correct answer = C. Because this patient has just been diagnosed with COPD and sleep apnea, his risk for opioid-induced respiratory depression is greater. Since the pain is controlled and no side effects are reported, tapering off the opioids at this time is not the best answer. Because of the first-pass effect, naloxone is not clinically effective for management of an overdose when given orally. Therefore, the nasal spray is the best choice. Offering the at-home naloxone nasal spray, along with proper education, might be lifesaving if an overdose occurs. Providing proper education to the patient and caregivers on the importance of having the naloxone nasal spray at home and of calling emergency services is critical in case of an overdose situation.

21.9 A 6-year-old boy presents to the hospital for a tonsillectomy. The day after surgery, his pain levels remain elevated despite use of nonopioid pain medications. Which of the following opioids is considered a proper option based on current recommendations?

A. Tramadol
B. Meperidine
C. Codeine
D. Oxycodone

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Correct answer = D. Of the choices provided, oxycodone is the most appropriate opioid to consider. Both tramadol and codeine are contraindicated for use in children <18 years old after a tonsillectomy and/or adenoidectomy. Meperidine carries additional risks.

21. How often should dosage adjustments for methadone occur in the outpatient setting?

A. Every 1 to 2 days
B. Every 3 to 4 days
C. Every 5 to 7 days
D. Every 10 to 14 days

Correct answer = C. Methadone has a long half-life that can vary from 12 to 40 hours, but has been reported to be as long as 150 hours. To allow adequate time for methadone to achieve steady state, it is recommended that dose adjustments should occur only every 5 to 7 days in the outpatient setting. In the inpatient setting, doses might be adjusted in some situations every 2 to 3 days with very close monitoring.

POLE STAR

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22

CNS Stimulants

Jose A. Rey, Carol Motycka

I. OVERVIEW

Psychomotor stimulants and hallucinogens are two groups of drugs that act primarily to stimulate the central nervous system (CNS). The psychomotor stimulants cause excitement and euphoria, decrease feelings of fatigue, and increase motor activity. As a group, the psychomotor stimulants have diverse clinical uses and are also potential drugs of abuse, as are the CNS depressants (Chapter 16) and the opioids (Chapter 21). Figure 22.1 summarizes these CNS stimulants and related drugs. The hallucinogens produce profound changes in thought patterns and mood, with little effect on the brainstem and spinal cord. The hallucinogens are discussed in detail in Chapter 47.

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PSYCHOMOTOR STIMULANTS

Amphetamine ADDERALL, DYANAVEL, MYDAYIS
Armodafinil NUVIGIL
Caffeine CAFCIT, NO DOZ, VIVARIN
Cocaine GENERIC ONLY
Dexmethylphenidate FOCALIN
Dexmethylphenidate/ Serdexmethylphenidate AZSTARYS
Dextroamphetamine DEXEDRINE, ZENZEDI
Lisdexamfetamine VYVANSE
Methamphetamine DESOXYN
Methylphenidate CONCERTA, COTEMPLA, DAYTRANA, RITALIN
Modafinil PROVIGIL
Nicotine NICODERM CQ, NICORETTE, NICOTROL
Theophylline ELIXOPHYLLIN, THEO-24, THEOCHRON
Varenicline CHANTIX

NONSTIMULANT DRUGS FOR ADHD

Atomoxetine STRATTERA
Clonidine KAPVAY
Guanfacine INTUNIV
Viloxazine QELBREE

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Figure 22.1 Summary of central nervous system stimulants and nonstimulant drugs for attention deficit hyperactivity disorder (ADHD).

II. PSYCHOMOTOR STIMULANTS

A. Methylxanthines

The methylxanthines include *theophylline* [thee-OFF-i-lin], which is found in tea; *theobromine* [thee-oh-BROE-meen], which is found in cocoa; and *caffeine* [kaf-EEN]. *Caffeine*, the most widely consumed stimulant in the world, is found in highest concentration in certain coffee products (for example, espresso), but it is also present in tea, cola drinks, energy drinks, chocolate candy, and cocoa.

1. Mechanism of action: Several mechanisms have been proposed for the actions of methylxanthines, including translocation of extracellular calcium, increase in cyclic adenosine monophosphate and cyclic guanosine monophosphate caused by inhibition of phosphodiesterase, and blockade of adenosine receptors.

2. Actions

a. Central nervous system: The *caffeine* contained in one to two cups of coffee (100-200 mg) causes a decrease in fatigue and increased mental alertness as a result of stimulating the cortex and other areas of the brain. Consumption of 1.5 g of *caffeine* (12-15 cups of coffee) produces anxiety and tremors. The spinal cord is stimulated only by very high doses (2-5 g) of *caffeine.* Tolerance can rapidly develop to the stimulating properties of *caffeine*, and withdrawal consists of feelings of fatigue and sedation.

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b. Cardiovascular system: A high dose of *caffeine* has positive inotropic and chronotropic effects on the heart. [Note: Increased contractility can be harmful to patients with angina pectoris. In others, an accelerated heart rate can trigger premature ventricular contractions.]

c. Diuretic action: *Caffeine* has a mild diuretic action that increases urinary output of sodium, chloride, and potassium.

d. Gastric mucosa: Because methylxanthines stimulate secretion of gastric acid, individuals with peptic ulcers should avoid foods and beverages containing methylxanthines.

3. Therapeutic uses: *Caffeine* and its derivatives relax the smooth muscles of the bronchioles. *Theophylline* has been largely replaced by other agents, such as β_2 agonists and corticosteroids, for the treatment of asthma (see Chapter 41). *Caffeine* is also used in combination with the analgesics *acetaminophen* and *aspirin* for the management of headaches in both prescription and over-the-counter products. *Caffeine* is often used by the general public to maintain wakefulness and temporarily reduce fatigue.

4. Pharmacokinetics: The methylxanthines are well absorbed orally. *Caffeine* distributes throughout the body, including the brain. These drugs cross the placenta to the fetus and are secreted into the breast milk. All methylxanthines are metabolized in the liver, generally by the cytochrome P450 (CYP)1A2 pathway, and the metabolites are excreted in the urine.

5. Adverse effects: Moderate doses of *caffeine* cause insomnia, anxiety, and agitation. A high dosage is required for toxicity, which is manifested by emesis and convulsions. The lethal dose is 10 g of *caffeine* (about 100 cups of coffee), which induces cardiac arrhythmias. Lethargy, irritability, and

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headache occur in users who routinely consume more than 600 mg of *caffeine* per day (roughly six cups of coffee per day) and then suddenly stop.

B. Nicotine

Nicotine [NIK-o-teen] is the active ingredient in tobacco. Although this drug is not currently used therapeutically (except in smoking cessation therapy), *nicotine* remains important because it is second only to *caffeine* as the most widely used CNS stimulant, and it is second only to alcohol as the most abused drug. In combination with the tars and carbon monoxide found in cigarette smoke, *nicotine* represents a serious risk factor for lung and atherosclerotic cardiovascular disease and other illnesses.

1. Mechanism of action: In low doses, *nicotine* causes ganglionic stimulation by depolarization. At high doses, *nicotine* causes ganglionic blockade. *Nicotine* (or nicotinic) receptors exist at a number of sites in the CNS, which participate in the stimulant attributes of the drug.

2. Actions

a. Central nervous system: *Nicotine* is highly lipid soluble and readily crosses the blood–brain barrier. Cigarette smoking or administration of low doses of *nicotine* produces some degree of euphoria and arousal, as well as relaxation. It improves attention, learning, problem solving, and reaction time. High doses of *nicotine* result in central respiratory paralysis and severe hypotension caused by medullary paralysis (Figure 22.2). *Nicotine* is also an appetite suppressant.

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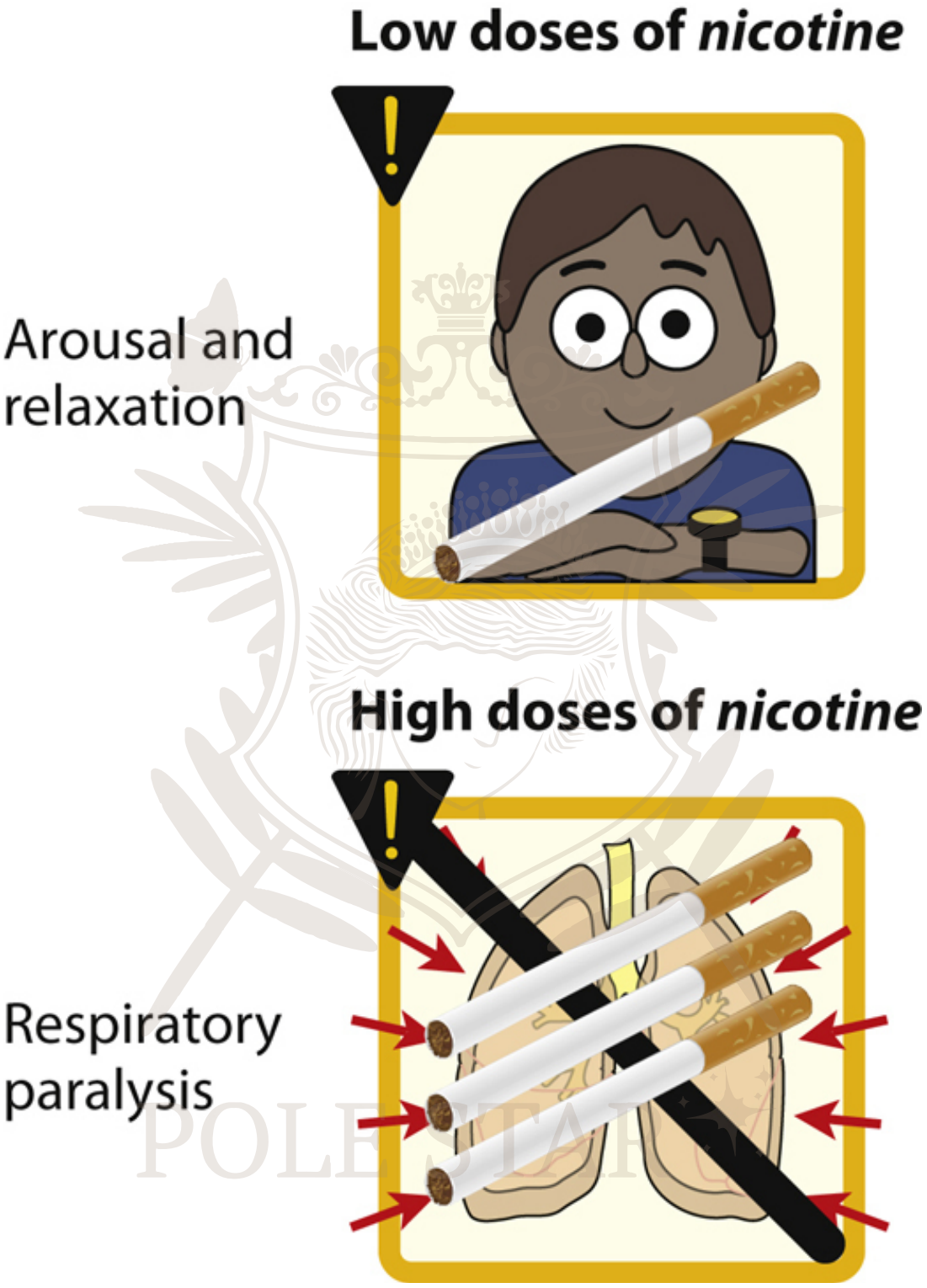

Figure 22.2 Actions of *nicotine* on the CNS.

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b. Peripheral effects: The peripheral effects of *nicotine* are complex. Stimulation of sympathetic ganglia as well as of the adrenal medulla increases blood pressure and heart rate. Thus, use of tobacco is particularly harmful in hypertensive patients. Many patients with peripheral artery disease experience an exacerbation of symptoms with smoking. In addition, *nicotine*-induced vasoconstriction can decrease coronary blood flow, adversely affecting a patient with angina. Stimulation of parasympathetic ganglia also increases motor activity of the bowel. At higher doses, blood pressure falls and activity ceases in both the gastrointestinal (GI) tract and bladder musculature as a result of a *nicotine*-induced block of parasympathetic ganglia.

3.Pharmacokinetics: Because *nicotine* is highly lipid soluble, absorption readily occurs via the oral mucosa, lungs, GI mucosa, and skin. *Nicotine* crosses the placental membrane and is secreted in the breast milk. By inhaling tobacco smoke, the average smoker takes in 1 to 2 mg of *nicotine* per cigarette. The acute lethal dose is 60 mg. More than 90% of the *nicotine* inhaled in smoke is absorbed. Clearance of *nicotine* involves metabolism in the lung and the liver and urinary excretion. Tolerance to the toxic effects of *nicotine* develops rapidly, often within days.

4.Adverse effects: The CNS effects of *nicotine* include irritability and tremors. *Nicotine* may also cause intestinal cramps, diarrhea, and increased heart rate and blood pressure. In addition, cigarette smoking increases the rate of metabolism for a number of drugs.

Clinical Application 22.1: Drug Interactions with Cigarette Smoking—Is It the Nicotine?

Many clinicians believe that it is *nicotine* that causes the induction of the CYP1A2 metabolizing enzymes and results in the drug interactions observed

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with cigarette smoking. It is actually the hydrocarbons from the inhalation of the smoke that cause the enzyme induction, and thus the reduction in plasma levels of certain common psychotropic medications, such as *olanzapine, clozapine*, and *haloperidol.* Cigarette smoking contributes to some patients having subtherapeutic (lower than needed for therapeutic effect) plasma levels in the outpatient setting. Therefore, cigarette smoking can pose a risk for loss of antipsychotic or mood-stabilizing effects of these medications, despite adherence to prescribed doses.

5.Withdrawal syndrome: As with the other drugs in this class, *nicotine* is an addictive substance, and physical dependence develops rapidly and can be severe (Figure 22.3). Withdrawal is characterized by irritability, anxiety, restlessness, difficulty concentrating, headaches, and insomnia. Appetite is affected, and GI upset often occurs. The transdermal patch and chewing gum containing *nicotine* have been shown to reduce *nicotine* withdrawal symptoms and to help smokers stop smoking. For example, the blood concentration of *nicotine* obtained from *nicotine* chewing gum is typically about one-half the peak level observed with smoking (Figure 22.4). Other forms of *nicotine* replacement used for smoking cessation include the inhaler, nasal spray, and lozenges. *Bupropion*, an antidepressant (Chapter 17), can reduce the craving for cigarettes/*nicotine*, assist in smoking cessation, and attenuate symptoms of withdrawal. These properties are likely due to its qualities of being a keto-amphetamine and a weak reuptake inhibitor of dopamine and norepinephrine.

POLE STAR

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Potential for withdrawal

Insomnia

Headache

Irritability

Potential for addiction

Nicotine

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Figure 22.3 *Nicotine* has potential for addiction and withdrawal.

POLE STAR

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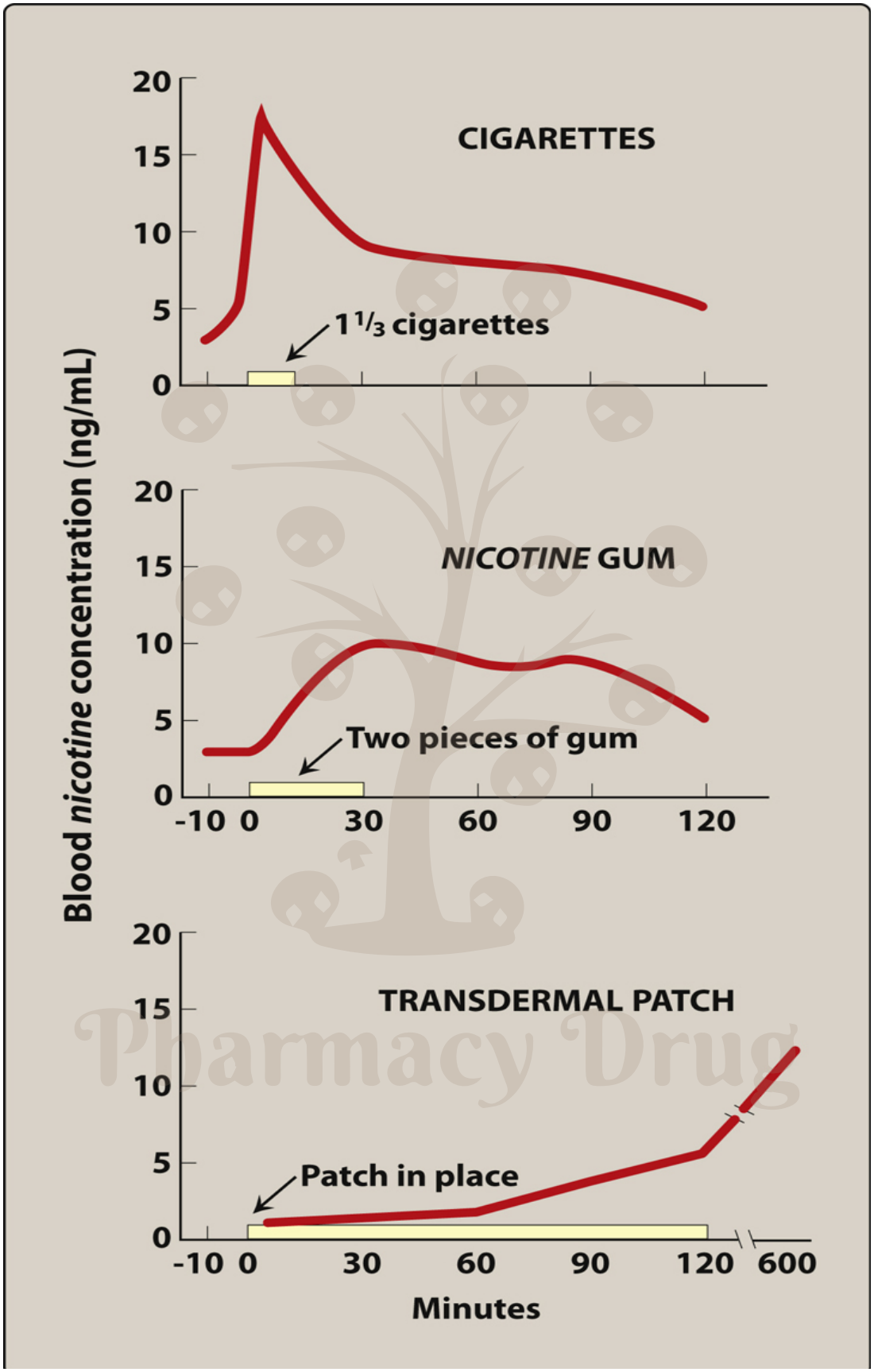

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Figure 22.4 Blood concentrations of *nicotine* in individuals who smoked cigarettes, chewed *nicotine* gum, or received *nicotine* by transdermal patch.Modified from N. L.Benowitz . Pharmacologic aspects of cigarette smoking and nicotine addiction. *N. Engl. J. Med*. 319: 1318 (1988).

C. Varenicline

Varenicline [ver-EN-e-kleen] is a partial agonist at neuronal nicotinic acetylcholine receptors in the CNS. Because *varenicline* is only a partial agonist at these receptors, it produces less euphoric effects than *nicotine* (*nicotine* is a full agonist). Thus, it is useful as an adjunct in the management of smoking cessation in patients with *nicotine* withdrawal symptoms. Patients taking *varenicline* should be monitored for suicidal thoughts, vivid nightmares, and mood changes.

D. Cocaine

Cocaine [koe-KANE] is a widely available and highly addictive drug. Because of its abuse potential, *cocaine* is classified as a Schedule II drug by the US Drug Enforcement Agency. The primary mechanism of action underlying the effects of *cocaine* is blockade of reuptake of the monoamines (norepinephrine, serotonin, and dopamine) into the presynaptic terminals. This potentiates and prolongs the CNS and peripheral actions of these monoamines. In particular, the prolongation of dopaminergic effects in the brain's pleasure system (limbic system) produces the intense euphoria that *cocaine* initially causes. Chronic intake of *cocaine* depletes dopamine. This depletion triggers craving for *cocaine* (Figure 22.5). A full description of *cocaine* and its effects is provided in Chapter 47.

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Figure 22.5 *Cocaine* and *amphetamine* have potential for addiction.

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E. Amphetamines

Amphetamine [am-FET-a-meen] is a sympathetic amine that shows neurologic and clinical effects similar to those of *cocaine. Dextroamphetamine* [dex-troe-am-FET-a-meen] is the major member of this class of compounds and is the d-isomer of the racemic mixture of amphetamines. *Lisdexamfetamine* [lis-dex-am-

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FET-a-meen] is a prodrug that is converted to l-lysine and the active component *dextroamphetamine* through the hydrolytic actions of red blood cells. *Methamphetamine* [meth-am-FET-a-meen] (also known as "*speed*") is a derivative of *amphetamine* available for prescription use.
3,4-Methylenedioxymethamphetamine (also known as MDMA, or ecstasy) is a synthetic derivative of *methamphetamine* with both stimulant and hallucinogenic properties (see Chapter 47).

1. Mechanism of action: As with *cocaine*, the effects of *amphetamine* on the CNS and peripheral nervous system are indirect. That is, both depend upon an elevation of the level of catecholamine neurotransmitters in synaptic spaces. *Amphetamine*, however, achieves this effect by releasing intracellular stores of catecholamines (Figure 22.6). Because *amphetamine* also inhibits monoamine oxidase (MAO) and is a weak reuptake transport inhibitor, high levels of catecholamines are present in synaptic spaces. Despite different mechanisms of action, the behavioral effects of *amphetamine* and its derivatives are similar to those of *cocaine*.

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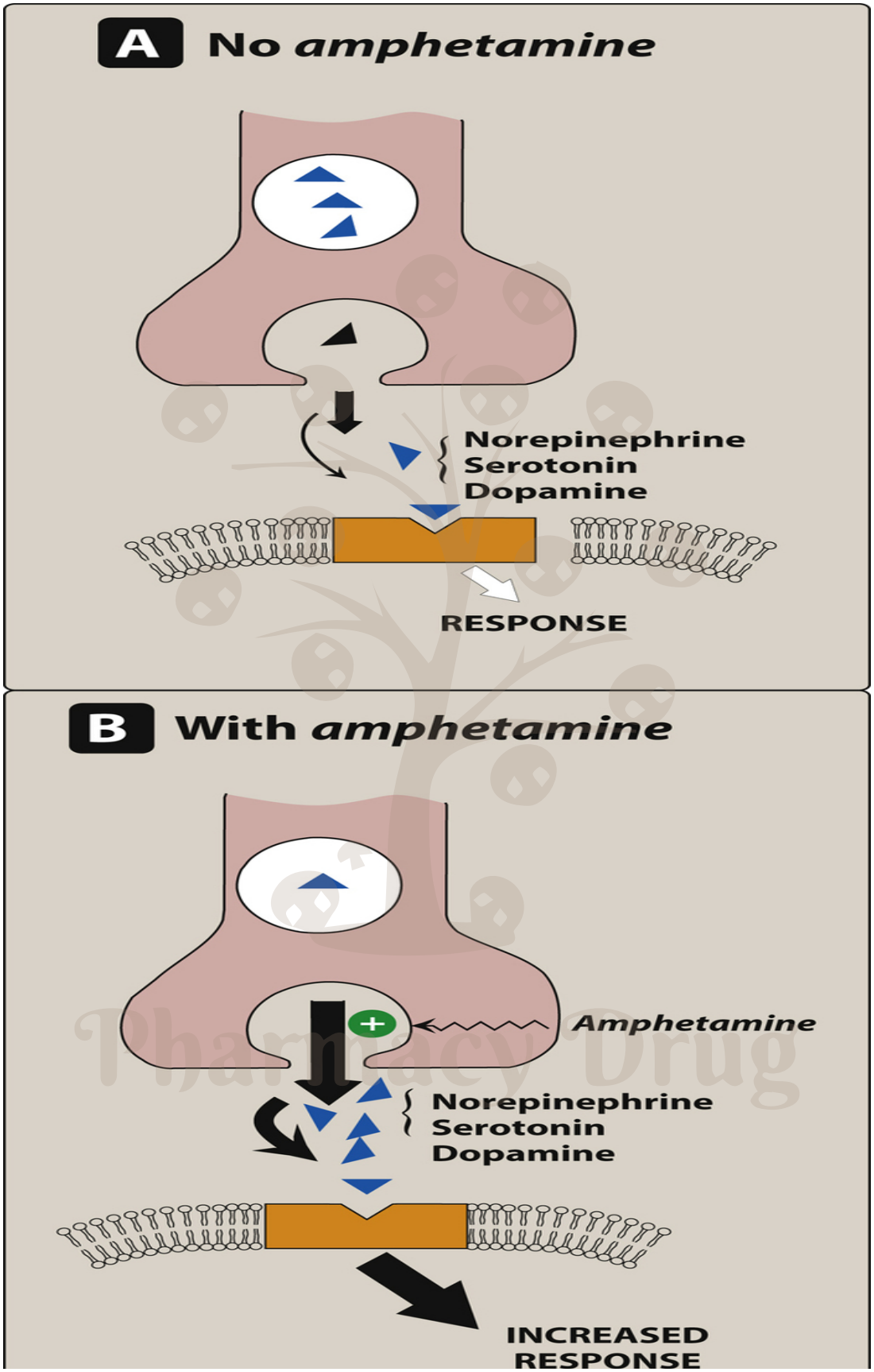

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Figure 22.6 Mechanism of action of *amphetamine*.

2. Actions

a. Central nervous system: The major behavioral effects of *amphetamine* result from a combination of its dopamine and norepinephrine release–enhancing properties. *Amphetamine* stimulates the entire cerebrospinal axis, cortex, brainstem, and medulla. This leads to increased alertness, decreased fatigue, depressed appetite, and insomnia. The CNS stimulant effects of *amphetamine* and its derivatives have led to their use in the treatment of hyperactivity in children, narcolepsy, and obesity. At high doses, psychosis and convulsions may occur.

b. Sympathetic nervous system: In addition to marked action on the CNS, *amphetamine* acts on the adrenergic system, indirectly stimulating the receptors through norepinephrine release.

3. Therapeutic uses: Factors that limit the therapeutic usefulness of *amphetamine* include psychological and physiologic dependence.

a. Attention deficit hyperactivity disorder: Children with attention deficit hyperactivity disorder (ADHD) are hyperkinetic and lack the ability to be involved in any activity for longer than a few minutes. *Dextroamphetamine*, *lisdexamfetamine*, *methamphetamine*, and the *mixed amphetamine salts* are stimulant drugs that help improve attention span and alleviate many of the behavioral problems associated with this syndrome, in addition to reducing hyperkinesia. Stimulants are considered first-line agents in the treatment of ADHD. The stimulant drugs have

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abuse potential and are classified as Schedule II controlled substances.

b. Narcolepsy: Narcolepsy is a relatively rare sleep disorder that is characterized by uncontrollable bouts of sleepiness during the day. The sleepiness can be treated with drugs, such as the *mixed amphetamine salts, methylphenidate*, *modafinil*, or *armodafinil* (see below).

c. Appetite suppression: *Phentermine* and *diethylpropion* are sympathomimetic amines that are related structurally to *amphetamine.* These agents are used for appetite suppressant effects in the management of obesity. See Section III for more information on these drugs and other agents used for weight loss in the management of obesity. [Note: *Lisdexamfetamine* is also approved for binge eating disorder.]

4.Pharmacokinetics: *Amphetamine* is completely absorbed from the GI tract, metabolized by the liver, and excreted in the urine. *Amphetamine* abusers often administer the drug by IV injection and/or by smoking. The euphoria caused by *amphetamine* lasts 4 to 6 hours, or four- to eightfold longer than the effects of *cocaine*.

5.Adverse effects: The amphetamines may cause addiction, leading to dependence, tolerance, and drug-seeking behavior. In addition, they have the following undesirable effects:

a. CNS effects: Adverse effects of *amphetamine* usage include insomnia, irritability, weakness, dizziness, tremor, and hyperactive reflexes (Figure 22.7). *Amphetamine* can also cause confusion, delirium, panic states, and suicidal tendencies, especially in mentally ill patients. [Note: Benzodiazepines, such as *lorazepam*, are often used in the management of agitation and CNS stimulation secondary to *amphetamine* overdose.] Chronic

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amphetamine use produces a state of "*amphetamine* psychosis" that resembles the psychotic episodes associated with schizophrenia. Long-term *amphetamine* use is associated with psychological and physical dependence, whereas tolerance to its effects may occur within a few weeks. The anorectic effect of *amphetamine* is due to action in the lateral hypothalamic feeding center.

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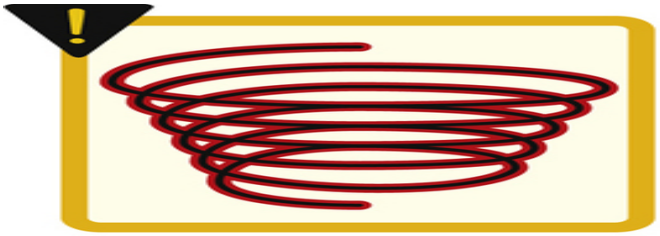
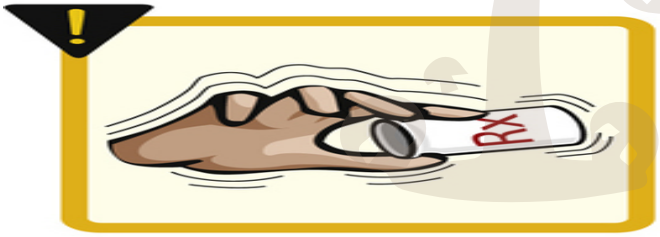


Vertigo

Hypertension

Insomnia

Confusion



Potential
for addiction

Nausea

Diarrhea

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Figure 22.7 Adverse effects of amphetamines and *methylphenidate*.

b. Cardiovascular effects: In addition to causing CNS effects, *amphetamine* may cause palpitations, cardiac arrhythmias, hypertension, anginal pain, and circulatory collapse. The cardiovascular adverse effects have contributed to sudden cardiac death in persons with underlying cardiac abnormalities or risks that may have not been recognized prior to stimulant use. Headache, chills, and excessive sweating may also occur.

c. Gastrointestinal effects: *Amphetamine* acts on the GI system, causing anorexia, nausea, vomiting, abdominal cramps, and diarrhea.

d. Contraindications: Patients with hypertension, cardiovascular disease, hyperthyroidism, glaucoma, or a history of drug abuse or those taking MAO inhibitors should not be treated with *amphetamine*.

F. Methylphenidate

Methylphenidate and its pharmacologically active isomer *dexmethylphenidate* [dex-meth-il-FEN-i-date] have CNS stimulant properties similar to those of *amphetamine* and are often used in the treatment of ADHD. Both *methylphenidate* and *dexmethylphenidate* have abuse potential and are classified as Schedule II controlled substances. *Serdexmethylphenidate* is a prodrug that is converted to *dexmethylphenidate* after ingestion.

1. Mechanism of action: Children with attention deficit disorder (ADD) or ADHD may produce weak dopamine signals, which suggests that activities that were once interesting now provide fewer rewards to these children. *Methylphenidate* is a dopamine and norepinephrine transport inhibitor and may act by increasing both dopamine and

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norepinephrine in the synaptic cleft. [Note: *Atomoxetine* [AT-oh-MOX-ih-teen], *viloxazine* [vi-LOX-a-zeen], *guanfacine,* and *clonidine* are nonstimulant drugs approved for ADHD in children and adults. Unlike *methylphenidate*, which blocks dopamine reuptake more than norepinephrine reuptake, *atomoxetine* and *viloxazine* are more selective for inhibition of norepinephrine reuptake. *Guanfacine* and *clonidine* are centrally acting α2-adrenoceptor agonists (see Chapter 6). Nonstimulant drugs for ADHD are not considered habit forming and are not controlled substances.]

2. Therapeutic uses: *Methylphenidate* is commonly used in the treatment of ADHD. *Dexmethylphenidate* and *dexmethylphenidate/serdexmethylphenidate* are also used for management of ADHD. *Methylphenidate* is also effective in the treatment of narcolepsy. Unlike *methylphenidate*, *dexmethylphenidate* is not indicated in the treatment of narcolepsy.

3. Pharmacokinetics: Both *methylphenidate* and *dexmethylphenidate* are readily absorbed after oral administration. *Methylphenidate* is available in extended-release oral formulations and as a transdermal patch for once-daily application. The de-esterified product, ritalinic acid, is excreted in urine.

4. Adverse effects: GI adverse effects are the most common and include abdominal pain and nausea. Other reactions include anorexia, insomnia, nervousness, and fever. Cardiac adverse effects and risks are similar to amphetamines. In patients with epilepsy, *methylphenidate* may increase seizure frequency.

G. Modafinil and armodafinil

Modafinil [moe-DA-fi-nil] and its R-enantiomer derivative, *armodafinil* [ar-moe-DA-fi-nil], are considered first-line agents for the treatment of narcolepsy. *Modafinil* promotes wakefulness, but

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it produces less psychoactive and euphoric effects and fewer alterations in mood, perception, thinking, and feelings compared with other CNS stimulants. The mechanism of action remains unclear but may involve the adrenergic and dopaminergic systems. *Modafinil* is well distributed throughout the body and undergoes elimination via hepatic metabolism and excretion in the urine. Headaches, nausea, and nervousness are the primary adverse effects. *Modafinil* and *armodafinil* may have some potential for abuse and physical dependence, and both are classified as controlled substances. [Note: Nonstimulant drugs indicated for the treatment of narcolepsy and excessive daytime sleepiness that may occur secondary to medical conditions such as sleep apnea are *solriamfetol* [SOL-ri-AM-fe-tol], a dopamine and norepinephrine reuptake inhibitor, and *pitolisant* [pi-TOL-i-sant], an antagonist/inverse agonist for histamine-3 receptors.]

III. DRUGS FOR OBESITY

Obesity is considered a body mass index (BMI) of 30 kg/m^2 or greater. Obesity is due in part to an energy imbalance, where caloric consumption exceeds caloric expenditure. However, it is now well understood that genetics, metabolism, behavior, environment, culture, and socioeconomic status play a role, as well. An individual with a BMI greater than 30 or greater than 27 with other comorbidities, such as hypertension and diabetes, is a potential candidate for pharmacologic treatment of obesity. Drugs for obesity are considered effective if they demonstrate at least a 5% greater reduction in body weight as compared with placebo (no treatment). Many of the available agents for weight loss are classified as anorexiants, or appetite suppressants. The anorexiants currently approved and used most commonly for weight loss include *phentermine* and *diethylpropion.* Several other anorexiants are used off-label for the management of weight loss; however, a discussion of those agents is beyond the scope of this chapter. A summary of medications used to treat obesity is provided in Figure 22.8.

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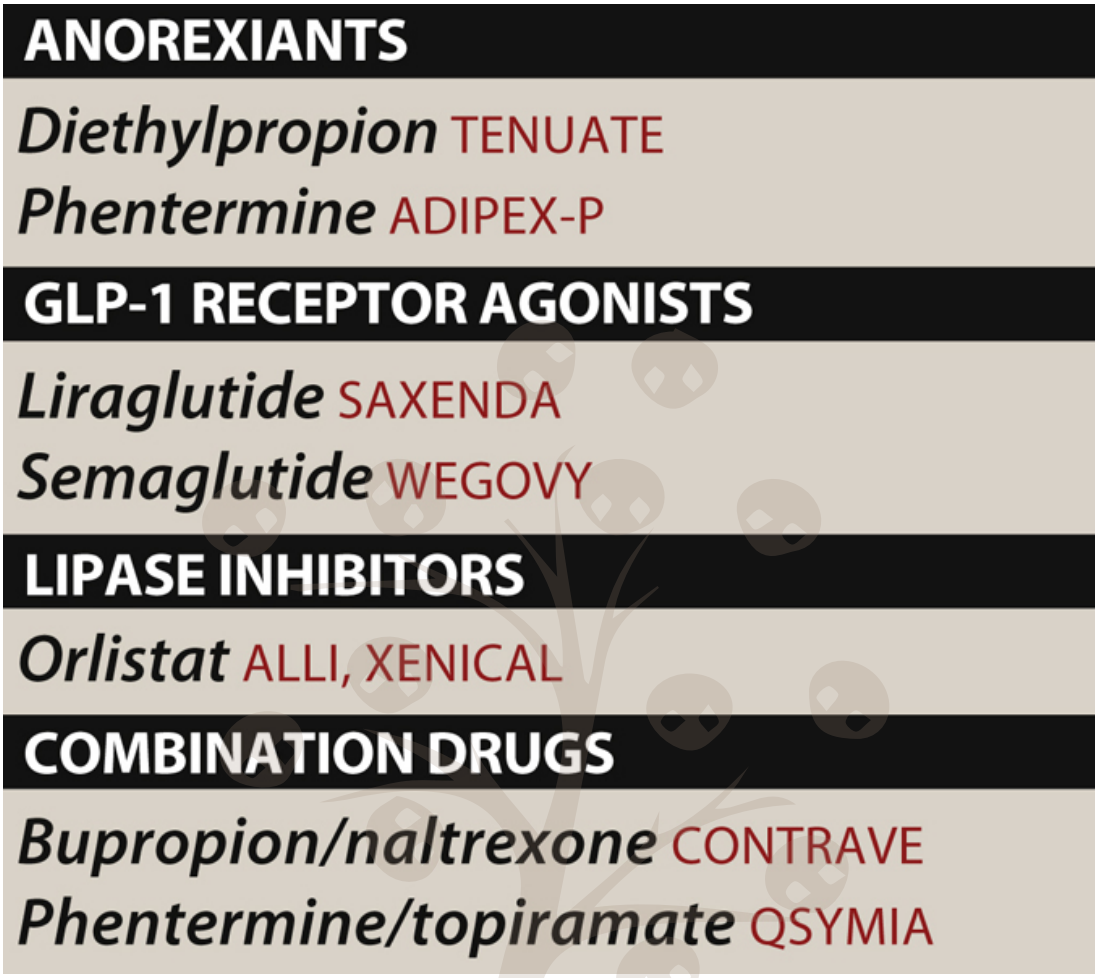

Figure 22.8 Summary of drugs used in the treatment of obesity.GLP-1 = glucagon-like peptide-1.

A. Anorexiants/Appetite suppressants

Phentermine [FEN-ter-meen] and *diethylpropion* [dye-eth-ill-PROE-pee-on] are CNS stimulants that are used as appetite suppressants. They exert pharmacologic action by increasing the release of norepinephrine and dopamine from the nerve terminals and by inhibiting reuptake of these neurotransmitters, thereby increasing levels of the neurotransmitters in the brain. The increase in norepinephrine signals a “fight-or-flight” response by the body, which, in turn, decreases appetite. Tolerance to the weight loss effect of these agents develops within weeks, and

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weight loss typically plateaus. An increase in the dosage generally does not result in further weight loss, and discontinuation of the drug is usually recommended once the plateau is reached. Therefore, these agents are indicated for the short-term management of weight loss. The anorexiants are classified as controlled substances due to the potential for dependence or abuse. Dry mouth, headache, insomnia, and constipation are common adverse effects. Heart rate and blood pressure may be increased with these agents. Therefore, these drugs should be avoided in patients with a history of uncontrolled hypertension, cardiovascular disease, arrhythmias, heart failure, or stroke. Concomitant use of anorexiants with monoamine oxidase inhibitors (MAOIs) or other sympathomimetics should be avoided.

B. Lipase inhibitor

Orlistat [OR-lih-stat] is the only agent in a class of antiobesity drugs known as lipase inhibitors. It is indicated for weight loss or chronic weight maintenance. *Orlistat* is a pentanoic acid ester that inhibits gastric and pancreatic lipases, thus decreasing the breakdown of dietary fat into smaller molecules that can be absorbed. Administration of *orlistat* decreases fat absorption by approximately 30%. The loss of calories from decreased absorption of fat is the main cause of weight loss. Figure 22.9 shows the weight loss effects of *orlistat* treatment. The clinical utility of *orlistat* is limited by gastrointestinal adverse effects, including oily spotting, flatulence with discharge, fecal urgency, and increased defecation. These effects may be minimized through a low-fat diet and the concomitant use of *cholestyramine.* *Orlistat* is contraindicated in pregnancy and in patients with chronic malabsorption syndrome or cholestasis. The drug also interferes with the absorption of fat-soluble vitamins and β-carotene. Patients should be advised to take a multivitamin supplement that contains vitamins A, D, E, and K and β-carotene. *Orlistat* can also interfere with the absorption of other medications, such as *amiodarone*, *cyclosporine*, and *levothyroxine*, and clinical response to these medications should

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be monitored if *orlistat* is initiated. The dose of *levothyroxine* should be separated from *orlistat* by at least 4 hours.

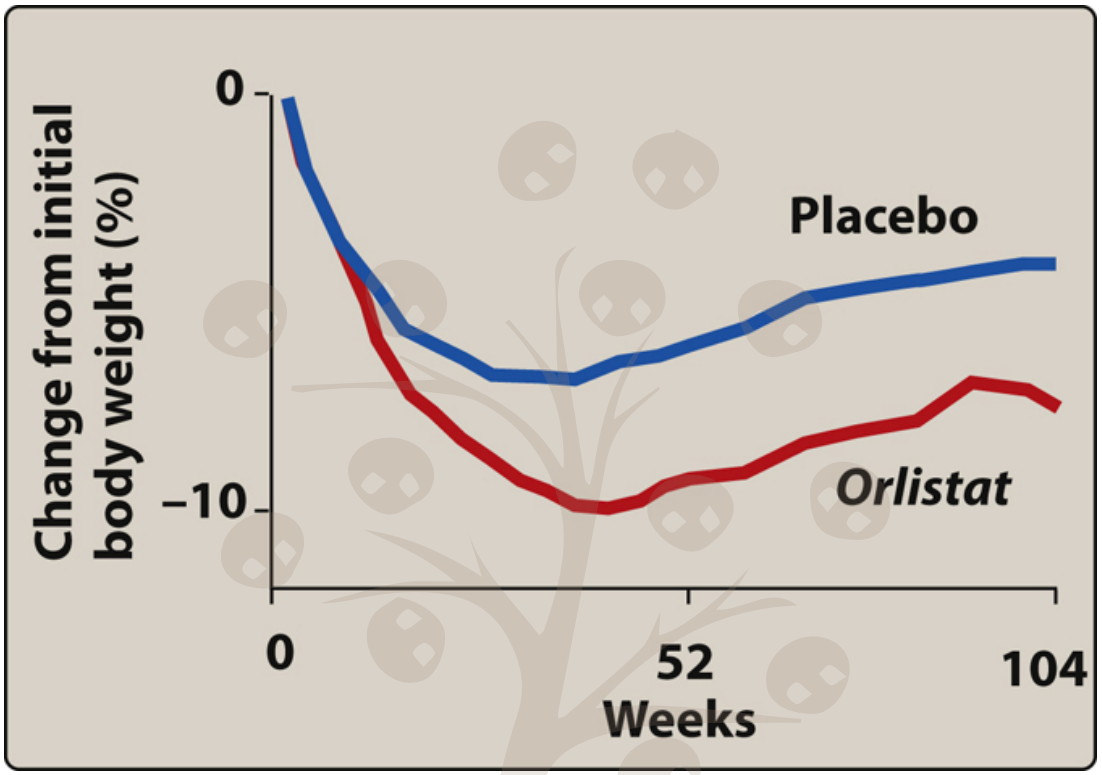

Figure 22.9 Effect of *orlistat* treatment on body weight.

C. Glucagon-like peptide-1 receptor agonists

Liraglutide and *semaglutide* are injectable glucagon-like peptide-1 (GLP-1) receptor agonists that are indicated for chronic weight management. GLP-1 is important in the regulation of appetite and food intake, and administration of these agents reduces hunger, thereby leading to decreased caloric intake and weight loss. *Liraglutide* is dosed daily and *semaglutide* has a once-weekly dosing schedule. GLP-1 receptor agonists are also indicated for the treatment of type 2 diabetes (see Chapter 24).

D. Combination therapies

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The combination of *phentermine* and *topiramate* is used for long-term treatment of obesity. Initial studies of the anticonvulsant *topiramate* observed weight loss in patients taking the drug. Because of the sedating effects of *topiramate*, the stimulant *phentermine* was added to counteract sedation and promote additional weight loss through appetite suppression. If a patient does not achieve a 5% weight loss after 12 weeks on the maximum dose of this combination, then use should be discontinued. It is also important to note that this agent should not be stopped abruptly as seizures may be precipitated. *Topiramate* has been associated with significant birth defects including cleft palate, and, thus, the combination of *phentermine*/*topiramate* is contraindicated in pregnancy and special precautions must be taken in order to avoid pregnancy during the use of this agent. *Bupropion* and *naltrexone* is another combination therapy used for chronic weight management. The combination therapy works through regulation of the mesolimbic reward system. *Bupropion/naltrexone* is contraindicated in uncontrolled hypertension. Important characteristics of the drugs for obesity are summarized in Figure 22.10.

POLE STAR

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DRUG	TARGET	MECHANISM OF ACTION	PHARMACOKINETICS	ADVERSE EFFECTS
Bupropion + naltrexone	*Bupropion:* CNS–POMC neuron stimulation *Naltrexone:* CNS—blocks autoinhibitory feedback of the hypothalamic melanocortin system	Combination regulates the mesolimbic reward system and results in appetite suppression	*Bupropion*: Metabolism in the liver; inhibitor of CYP2D6 *Naltrexone*: Excretion through the kidneys	Nausea, headache, dry mouth, dizziness, constipation, suicidal ideation
Liraglutide *Semaglutide*	GLP-1 receptor agonist	Slows gastric emptying and increases satiety	Metabolized similar to large proteins; no specific organ of elimination	Nausea and vomiting, pancreatitis, hypoglycemia, acute gall bladder disease, elevated heart rate, suicidal ideation
Orlistat	GI system—inhibits gastric and pancreatic lipase	Fat absorption decreased by ~30%, which decreases overall caloric intake	Minimal systemic absorption	GI symptoms such as oily spotting, flatulence, fecal urgency, and increased defecation
Phentermine	CNS—increase in NE and dopamine release and reuptake inhibition	Appetite suppression	Excretion through the kidneys	Dry mouth, headache, insomnia, constipation Possible heart rate and blood pressure increases
Diethylpropion	CNS—increase in NE and dopamine release and reuptake inhibition	Appetite suppression	Excretion mainly through the kidneys	Dry mouth, headache, insomnia, constipation Possible heart rate and blood pressure increases
Phentermine + topiramate	*Phentermine:* CNS—increase in NE and dopamine release and reuptake inhibition *Topiramate:* CNS—increase in GABA	Appetite suppression and increased satiety	Excretion primarily through the kidneys with limited hepatic metabolism	Paresthesia, altered taste, dizziness, insomnia, dry mouth, constipation Contraindicated in pregnancy

Figure 22.10 Characteristics of the medications for obesity.CNS = central nervous system; GABA = γ-aminobutyric acid; GI = gastrointestinal; GLP = glucagon-like peptide; NE = norepinephrine; POMC = proopiomelanocortin.

Clinical Application 22.2 Management of Obesity

Obesity is a condition that affects approximately one-third of the population in the United States and is becoming a growing problem throughout the world. Obesity is responsible for a multitude of comorbidities, including hypertension, diabetes, coronary artery disease, and depression. Treatment should be multifactorial and should include lifestyle modifications for diet and exercise, behavioral therapy, and medications when needed. Drug therapy for the treatment of obesity should be considered when diet and exercise have been unsuccessful. Because agents for the treatment of obesity are associated with significant risks, they are only recommended for patients with a BMI greater than 30 kg/m^2 or greater than 27 kg/m^2 with other comorbidities, such as hypertension and diabetes. Agents for obesity provide the most benefit when used in conjunction with behavioral therapy and continuation of lifestyle modifications.

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Chapter Summary

- CNS stimulants, also referred to as psychostimulants, are effective treatments for ADD/ADHD, narcolepsy, obesity, and binge eating disorder.
- Most of the available CNS stimulants have inhibition of presynaptic dopamine or norepinephrine reuptake as a principle mechanism of action.
- CNS stimulants have a high risk for abuse and dependence. Many commonly abused drugs such as *nicotine*, *caffeine*, and *cocaine* are CNS stimulants, and the prescription-only psychostimulants also have a high risk for abuse.
- The CNS stimulants *caffeine* and *nicotine* remain two of the most commonly abused drugs in society due to ease of access and addictive qualities, respectively.
- Individuals receiving prescription CNS stimulants should be medically evaluated prior to initiation of therapy, due to the high risk of these agents worsening common medical conditions such as hypertension and heart disease.
- Many currently used psychostimulants for the treatment of ADHD have been used orally for many years. Most new treatments for ADHD are focused on development of innovative formulations, such as transdermal or extended-release oral agents in liquid suspensions or disintegrating tablets.
- CNS stimulants, such as *amphetamine*, *dextroamphetamine, methylphenidate*, and *dexmethylphenidate* are considered first-line agents for the treatment of ADHD, along with behavioral interventions.
- The CNS stimulants *modafinil* and *armodafinil* are considered first-line therapy for the management of narcolepsy, with the amphetamines and *methylphenidate* reserved for more severe cases.
- Drugs for obesity should be used in conjunction with lifestyle modifications and behavioral therapy for optimal treatment.
- Drugs for the treatment of obesity include *phentermine*, *diethylpropion, orlistat*, *liraglutide*, *semaglutide*, and combination medications including *phentermine/topiramate* and *bupropion/naltrexone*.
- Use of *phentermine* or *phentermine*-containing combinations should be avoided in patients with uncontrolled hypertension due to the potential for increased blood pressure and heart rate with their use.
- *Orlistat* is associated with many gastrointestinal adverse effects (for example, oily spotting, flatulence with discharge, and fecal urgency) which limit its clinical use.

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STUDY QUESTIONS

Choose the ONE best answer.

22.1 Amphetamines may be used in patients with which of the following conditions?

A. Cardiovascular disease
B. Hypertension
C. Hyperthyroidism
D. Obesity

Correct answer = D. The use of amphetamines in the management of obesity should be closely monitored. Amphetamine analogs such as phentermine are approved for obesity. The other conditions are contraindications when considering the use of amphetamines.

22.2 A 10-year-old boy is sent to a pediatric neurologist for an evaluation due to poor performance and inability to pay attention in school. He has also been fighting with other children. He is given a diagnosis of ADHD with impulsivity and irritability. Which of the following is most appropriate for management of the ADHD?

A. Clonidine
B. Mirtazapine
C. Dextroamphetamine
D. Haloperidol

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Correct answer = C. Dextroamphetamine is the only stimulant medication in the list that is approved for ADHD. Symptoms like fighting may improve with haloperidol, and hyperactivity may improve with clonidine, but these agents would not improve the patient's academic performance and the underlying problems.

22.3 A 6-year-old girl with predominantly attention deficit symptoms, and not hyperactivity behaviors, requires an

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alternate treatment to address school and family problems due to her ADD, and she has failed adequate trials of amphetamines and methylphenidate formulations. Which of the following is an appropriate treatment option at this time?

A. Armodafinil
B. Atomoxetine
C. Lisdexamfetamine
D. Dexmethylphenidate

Correct answer = B. Atomoxetine is considered an appropriate second-line agent after patients have failed the psychostimulants from both classes of amphetamines and methylphenidate. The isomers of these respective groups of stimulants are not expected to have superior efficacy over the racemic mixtures. Armodafinil is used for narcolepsy.

22.4 Which of the following is a common adverse effect of amphetamines?

A. Bradycardia
B. Somnolence
C. Constipation
D. Hypertension

Correct answer = D. Hypertension is a possible adverse effect that warrants caution, especially in individuals with risk factors for increased blood pressure. Amphetamines cause tachycardia (not bradycardia), insomnia (not somnolence), and diarrhea (not constipation).

22.5 Which of the following agents is considered a first-line treatment of narcolepsy?

A. Galantamine
B. Atomoxetine
C. Temazepam
D. Modafinil

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Correct answer = D. Modafinil is the only drug listed that is approved for narcolepsy. Temazepam is indicated for insomnia, galantamine for Alzheimer disease, and atomoxetine for ADHD.

22.6 A 35-year-old man is interested in quitting smoking. In previous quit attempts, he has tried nicotine gum, the nicotine patch, and the "cold turkey" method. He has been unsuccessful in each of these attempts and resumed smoking within 4 to 6 weeks. Which of the following may be useful to assist in his attempt to quit smoking?

A. Varenicline
B. Dextroamphetamine
C. Lorazepam
D. Methylphenidate

Correct answer = A. Varenicline is approved as an adjunctive treatment option for the management of nicotine dependence. It is believed to attenuate the withdrawal symptoms of smoking cessation, although monitoring is needed for changes in psychiatric status, including suicidal ideation. The use of dextroamphetamine, lorazepam, and methylphenidate bring the risk of addiction to another substance with abuse potential.

22.7 Which of the following treatment options for the management of ADHD carries the lowest risk for abuse or addiction?

A. Viloxazine
B. Dextroamphetamine
C. Dexmethylphenidate
D. Methamphetamine

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Correct answer = A. Viloxazine is the only agent listed that is not labeled as a controlled substance, and it does not have the risk for abuse that dextroamphetamine, dexmethylphenidate, or methamphetamine has.

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22.8 A patient who weighs 85 kg and has a body mass index of 40 kg/m^2 is diagnosed with binge eating disorder and obesity and requires treatment. Which of the following is the most appropriate agent for this patient?

A. Fluoxetine
B. Lisdexamfetamine
C. Phentermine
D. Caffeine-containing over-the-counter appetite suppressants

Correct answer = B. Lisdexamfetamine is the only agent approved for the treatment of binge eating disorder (BED). Other formulations of dextroamphetamine or amphetamine have historically been used for weight loss in the management of obesity, even though none are currently approved for such use. Fluoxetine may cause an initial weight loss that is usually not sustained, and it is approved for the management of bulimia, which is a different kind of eating disorder. Phentermine is approved for the management of obesity only, not BED. Caffeine-containing products available over the counter (without a prescription) have minimal data supporting weight loss efforts and are not indicated for BED.

22.9 A fellow health care provider is concerned about prescribing orlistat to adolescent patients. Many of his adolescent patients are stopping the medication during the first month of treatment. Which of the following side effects is the most likely reason the adolescents are discontinuing orlistat?

A. Hypoglycemia
B. Suicidal ideation
C. Drowsiness
D. Fecal urgency

Correct answer = D. Fecal urgency is a common side effect with orlistat, along with several other GI disturbances. For adolescents, these side effects may be embarrassing and difficult to manage. It is important to counsel patients about the gastrointestinal side effects of orlistat, recommend a low-fat diet, and offer the use of cholestyramine to counteract the side effects. The other adverse

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effects listed have been observed with other obesity medications but not with orlistat.

22.10 A 38-year-old woman with a history of uncontrolled hypertension asks about recommendations for weight loss. Which of the following drugs should be excluded from the list of possible choices for this patient?

A. Phentermine
B. Orlistat
C. Liraglutide
D. Semaglutide

Correct answer = A. Phentermine should be avoided in patients with uncontrolled hypertension, since its stimulant effects can raise blood pressure and heart rate. The other agents do not have a contraindication with hypertension.

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Unit V:
Drugs Affecting the Endocrine System

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23

Pituitary and Thyroid

Shannon A. Miller, Christina E. DeRemer

I. OVERVIEW

The endocrine system releases hormones into the bloodstream, which carries chemical messengers to target cells throughout the body. The primary role is to direct and manage bodily activities. Due to varied functions, hormones have a much broader range of response times than do nerve impulses. Hormones require seconds to days, or longer, to cause a response that may last for weeks or months, whereas nerve impulses generally create a response within milliseconds. An important function of the hypothalamus is to connect the nervous system with the endocrine system via the pituitary gland. This chapter presents the central role of hypothalamic and pituitary hormones in regulating body functions. In addition, drugs affecting thyroid hormone synthesis and/or secretion are discussed (Figure 23.1). Chapters 24-26 focus on drugs that affect the synthesis and/or secretion of specific hormones and their actions.

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HYPOTHALAMIC AND ANTERIOR PITUITARY HORMONES

Corticotropin H.P. ACTHAR
Cosyntropin CORTROSYN
Follitropin alfa GONAL-F
Follitropin beta FOLLISTIM AQ
Goserelin ZOLADEX
Histrelin SUPPRELIN LA, VANTAS
Lanreotide SOMATULINE DEPOT
Leuprolide LUPRON
Menotropins MENOPUR
Nafarelin SYNAREL
Octreotide SANDOSTATIN
Somatropin HUMATROPE, GENOTROPIN
Urofollitropin BRAVELLE

POSTERIOR PITUITARY HORMONES

Desmopressin DDAVP
Oxytocin PITOCIN
Vasopressin (ADH) VASOSTRICT

DRUGS AFFECTING THE THYROID

Iodine and potassium iodide LUGOL'S SOLUTION
Levothyroxine SYNTHROID
Liothyronine CYTOMEL
Liotrix THYROLAR
Methimazole TAPAZOLE
Propylthiouracil (PTU) GENERIC ONLY

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Figure 23.1 Hormones and drugs affecting the hypothalamus, pituitary, and thyroid.

II. HYPOTHALAMIC AND ANTERIOR PITUITARY HORMONES

The pituitary gland is often called the “master gland” because it secretes important hormones that influence all cells and virtually all physiologic processes. The release of hormones is controlled by the hypothalamus via a signal sent in the form of releasing or inhibiting hormones. Releasing and inhibiting hormones reach the pituitary by the hypophyseal portal system (Figure 23.2). Each hypothalamic regulatory hormone controls the release of a specific hormone from the anterior pituitary. The interaction of the releasing hormones with receptors results in the activation of genes that promote the synthesis of protein precursors. The protein precursors then undergo posttranslational modification to produce hormones, which are released into the circulation. The hormones secreted by the pituitary are peptides or glycoproteins that act by binding to specific receptor sites on target tissues. Hormones of the anterior pituitary are administered intramuscularly (IM), subcutaneously, or intranasally because their peptidyl nature makes them susceptible to destruction by proteolytic enzymes of the digestive tract. Pituitary hormone preparations are currently used for specific hormonal deficiencies, although most of the agents have limited therapeutic applications.

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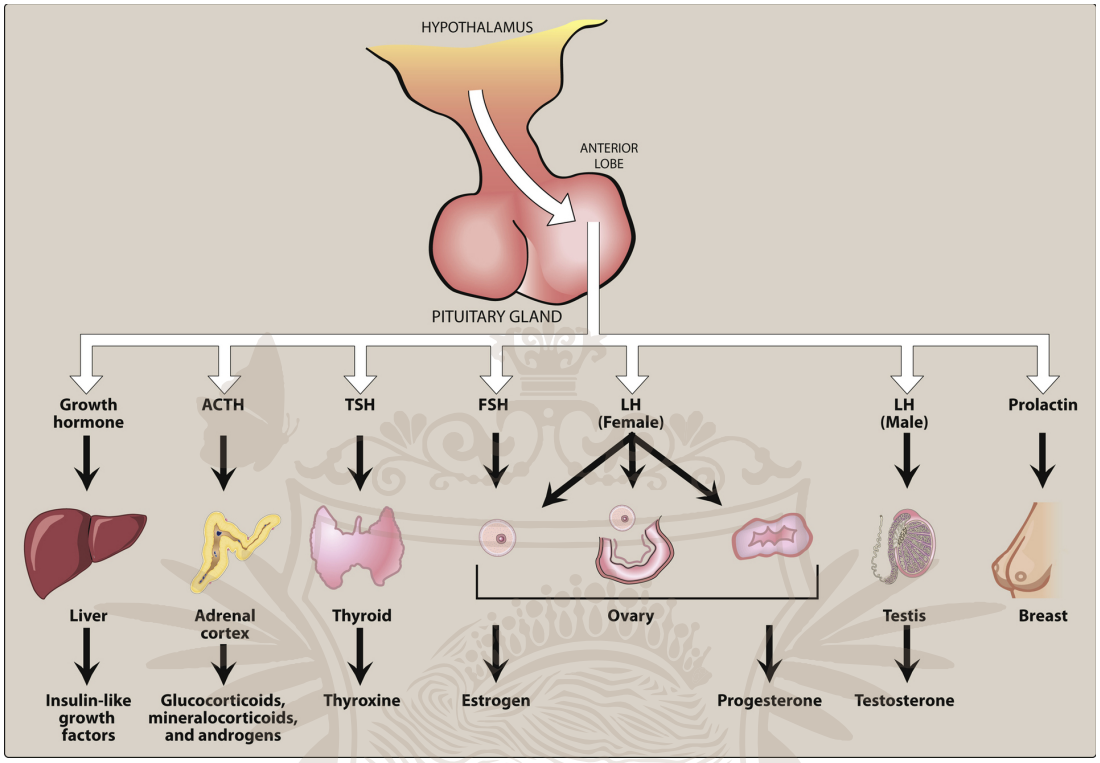

Figure 23.2 Anterior pituitary hormones.ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; LH = luteinizing hormone; TSH = thyroid-stimulating hormone.Modified from B. G.Katzung . *Basic and Clinical Pharmacology*. Appleton and Lange (1987); permission conveyed through Copyright Clearance Center, Inc.

A. Adrenocorticotropic hormone (corticotropin)

Corticotropin-releasing hormone (CRH) is responsible for the synthesis and release of the peptide proopiomelanocortin by the pituitary (Figure 23.3). Adrenocorticotropic hormone (ACTH) or *corticotropin* [kor-ti-koe-TROE-pin] is a product of the posttranslational processing of this precursor polypeptide. [Note: CRH is used diagnostically to differentiate between Cushing syndrome and ectopic ACTH-producing cells.] Normally, ACTH is released from the pituitary in pulses with an overriding diurnal rhythm, with the highest concentration occurring in early morning and the lowest in late evening. Stress stimulates its secretion,

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whereas cortisol acting via negative feedback suppresses its release, an important concept for diagnostic testing.

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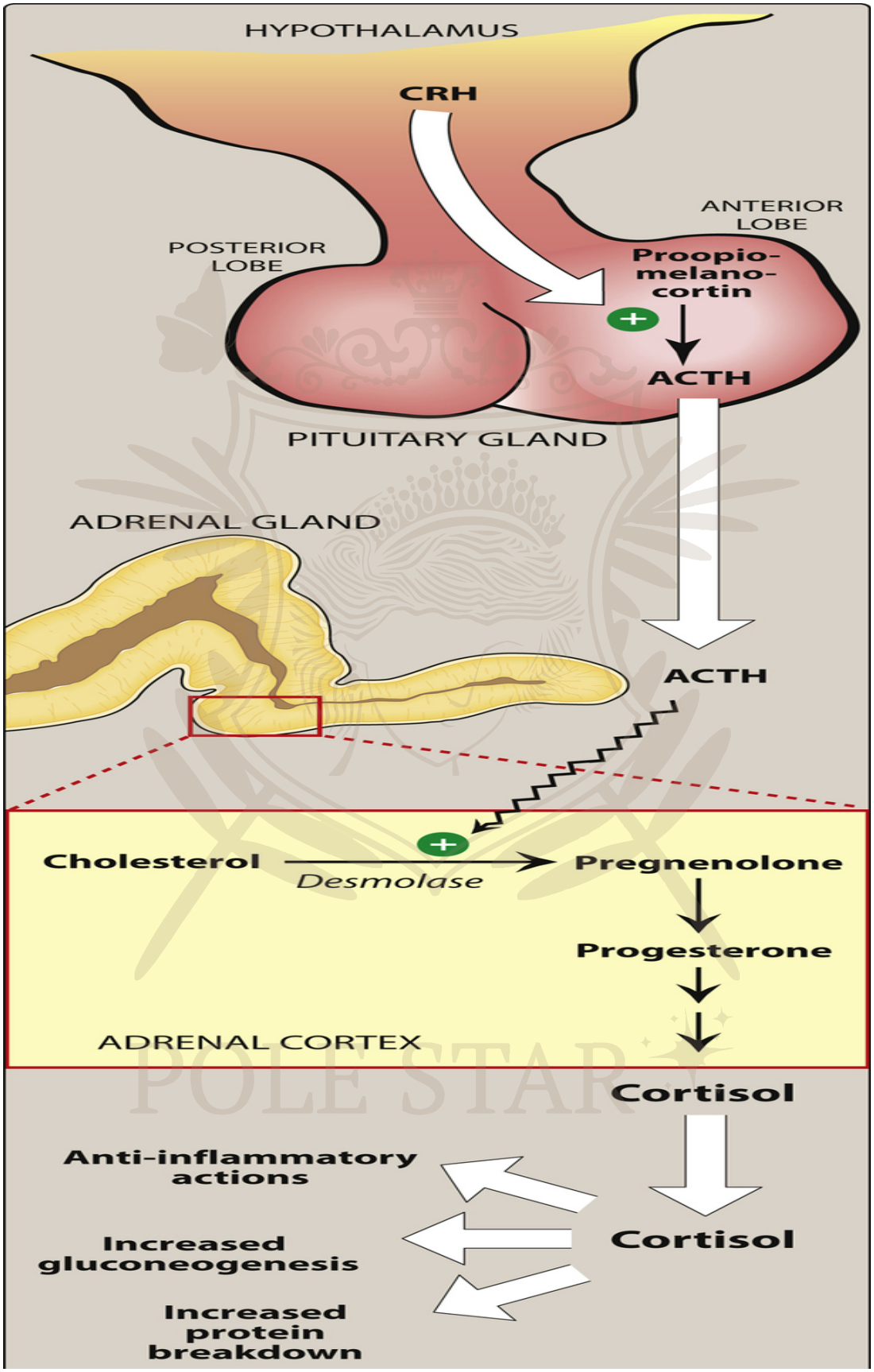
HYPOTHALAMUS
CRH
ANTERIOR LOBE
POSTERIOR LOBE
Proopio-melano-cortin
+
ACTH
PITUITARY GLAND
ADRENAL GLAND
ACTH
+
Cholesterol
Desmolase
Pregnenolone
Progesterone
ADRENAL CORTEX
Cortisol
Anti-inflammatory actions
Increased gluconeogenesis
Increased protein breakdown
Cortisol

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Figure 23.3 Secretion and actions of adrenocorticotropic hormone (ACTH).CRH = corticotropin-releasing hormone.

1. **Mechanism of action:** ACTH binds to receptors on the surface of the adrenal cortex, thereby activating G protein–coupled processes that ultimately stimulate the rate-limiting step in the adrenocorticosteroid synthetic pathway (cholesterol to pregnenolone; Figure 23.3). This pathway ends with the synthesis and release of adrenocorticosteroids and the adrenal androgens.

2. **Therapeutic uses:** The availability of synthetic adrenocorticosteroids with specific properties has limited the use of *corticotropin* mainly to serving as a diagnostic tool for differentiating between primary adrenal insufficiency (Addison disease, associated with adrenal atrophy) and secondary adrenal insufficiency (caused by inadequate secretion of ACTH by the pituitary). Therapeutic *corticotropin* preparations are extracts from the anterior pituitaries of domestic animals or synthetic human ACTH. The latter, *cosyntropin* [ko-sin-TROE-pin], is preferred for the diagnosis of adrenal insufficiency. ACTH is also used in the treatment of infantile spasms, multiple sclerosis, and resistant epilepsy.

3. **Adverse effects:** Short-term use of ACTH for diagnostic purposes is usually well tolerated. With longer use, toxicities are similar to glucocorticoids and include hypertension, peripheral edema, hypokalemia, emotional disturbances, bone loss, and increased risk of infection.

B. Growth hormone (somatotropin)

Somatotropin is released by the anterior pituitary in response to growth hormone (GH)-releasing hormone (Figure 23.4). Conversely, secretion of GH is inhibited by the hormone somatostatin (see below). Somatotropin influences a wide variety

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of biochemical processes (for example, cell proliferation and bone growth). GH is released in a pulsatile manner, with the highest levels occurring during sleep. With increasing age, GH secretion decreases, accompanied by a decrease in lean muscle mass. Synthetic human GH (*somatropin* [soe-mah-TROE-pin]) is produced using recombinant DNA technology.

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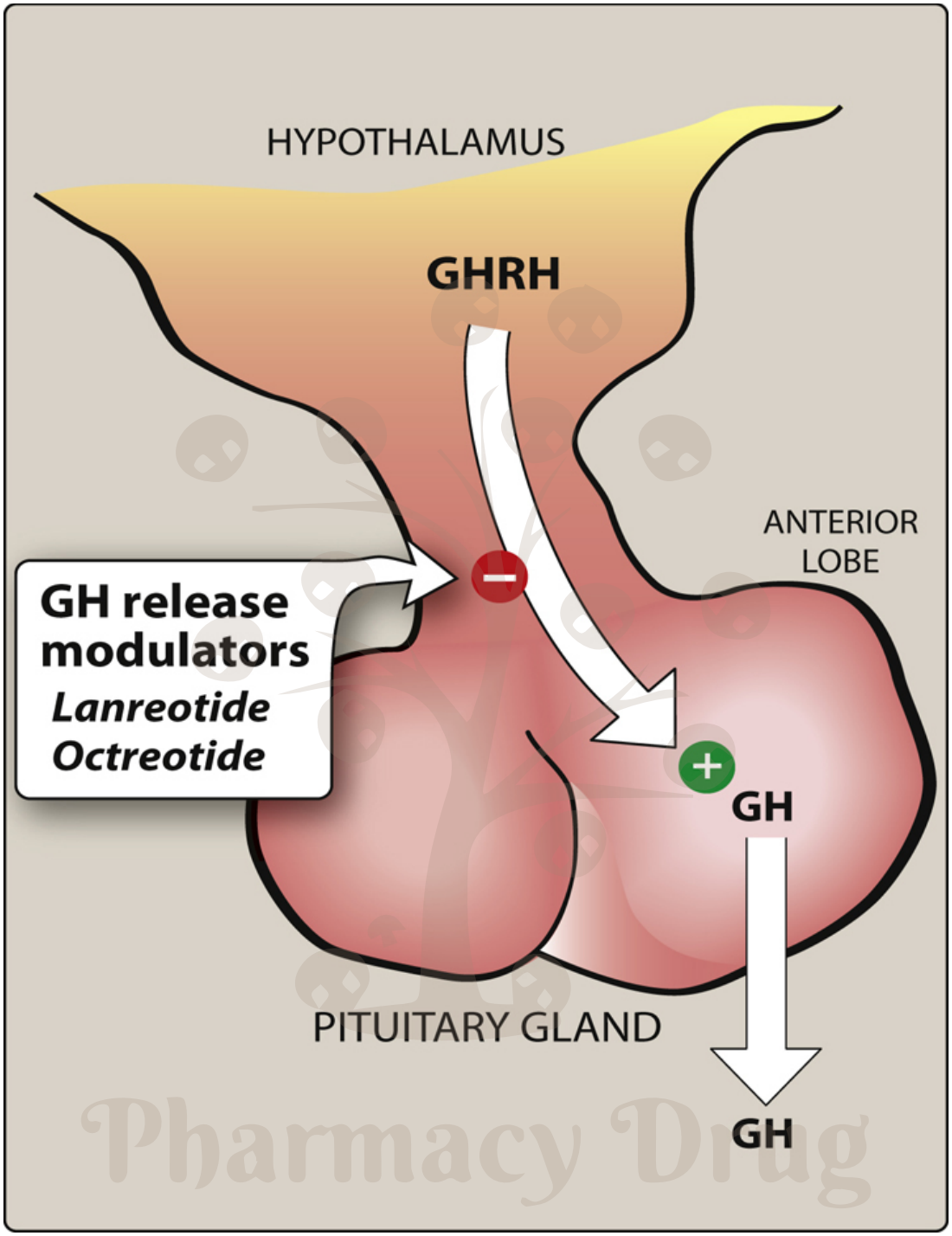

Figure 23.4 Secretion of growth hormone (GH).GHRH = growth hormone–releasing hormone.

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1.Mechanism of action: Although many physiologic effects of GH are exerted directly at its targets, others are mediated indirectly through the somatomedins—insulin-like growth factors 1 and 2 (IGF-1 and IGF-2). [Note: In acromegaly (a syndrome of excess GH due to a pituitary tumor or other hormone-secreting tumors), IGF-1 levels are consistently high, reflecting elevated GH.]

2.Therapeutic uses: *Somatropin* (recombinant human growth hormone) is used in the treatment of GH deficiency, growth failure in children, treatment of HIV-associated wasting/cachexia, and GH replacement in adults with confirmed deficiency. [Note: GH administered to adults increases lean body mass, bone density, and skin thickness and decreases adipose tissue. Many consider GH an "antiaging" hormone. This has led to off-label use of GH by older individuals and by athletes seeking to enhance performance.] *Somatropin* is administered by subcutaneous or IM injection. Although the half-life of GH is short (approximately 25 minutes), it induces release of IGF-1 from the liver, which is responsible for subsequent GH-like actions.

3.Adverse effects: Adverse effects of *somatropin* include pain at the injection site, edema, arthralgias, myalgias, nausea, and an increased risk of diabetes. *Somatropin* should not be used in pediatric patients with closed epiphyses, patients with diabetic retinopathy, or obese patients with Prader–Willi syndrome.

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Clinical Application 23.1: Use of Somatropin for Growth Hormone Deficiency

The most common place in therapy for *somatropin* (recombinant human growth hormone) is for the treatment of underdeveloped children with GH deficiency and other genetic or idiopathic causes of short stature. Untreated children with GH deficiency are categorized as having dwarfism or pituitary dwarfism. Children with GH deficiency often have short stature, delayed bone maturation,

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and central distribution of fat. Administration of *somatropin* promotes growth, increases bone mass, and decreases body fat. *Somatropin* should be continued until growth slows to less than 2.0 to 2.5 cm per year or the child reaches the target height. This agent should not be used to promote growth in adolescents where closure of the epiphyseal plates (growth plates at the end of each long bone) has already occurred. *Somatropin* may also be used in adults with confirmed GH deficiency due to surgery, trauma, radiation, or other causes. In adults, this agent has been used off-label to as an antiaging drug to reduce age-related decline in muscle mass. Use of *somatropin* for antiaging should be avoided, as the risks (carpal tunnel syndrome, joint pain, edema, and impaired glucose intolerance) outweigh any potential benefits.

C. Somatostatin (growth hormone–inhibiting hormone)

In the pituitary, somatostatin binds to receptors that suppress release of GH and thyroid-stimulating hormone (TSH). Originally isolated from the hypothalamus, somatostatin is a small polypeptide found in neurons throughout the body as well as in the intestine, stomach, and pancreas. Somatostatin inhibits release of not only GH but also insulin, glucagon, and gastrin. *Octreotide* [ok-TREE-oh-tide] and *lanreotide* [lan-REE-oh-tide] are synthetic analogs of somatostatin with longer half-lives. Depot formulations of these agents allow for administration every 4 weeks. These agents have found use in the treatment of acromegaly and in severe diarrhea/flushing episodes associated with carcinoid tumors. An intravenous infusion of *octreotide* is also used for the treatment of bleeding esophageal varices. Adverse effects of *octreotide* include bradycardia, diarrhea, abdominal pain, flatulence, nausea, and steatorrhea. Gallbladder emptying is delayed, and asymptomatic cholesterol gallstones can occur with long-term treatment. *Lanreotide* has a similar adverse effect profile.

D. Gonadotropin-releasing hormone

Pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus is essential for release of the gonadotropins follicle-stimulating hormone (FSH) and luteinizing

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hormone (LH) from the anterior pituitary. However, continuous administration of GnRH inhibits gonadotropin release through downregulation of GnRH receptors on the pituitary. Continuous administration of synthetic GnRH analogs, such as *leuprolide* [loo-PROE-lide], is effective in suppressing production of FSH and LH (Figure 23.5). Suppression of gonadotropins, in turn, leads to reduced production of gonadal steroid hormones (androgens and estrogens). Thus, these agents are effective in the treatment of prostate cancer (see Chapter 37), endometriosis, and precocious puberty. *Leuprolide* is also used to suppress the LH surge and prevent premature ovulation in women undergoing controlled ovarian stimulation protocols for the treatment of infertility. GnRH antagonists such as *cetrorelix* [set-roe-REL-iks] and *ganirelix* [ga-ni-REL-iks] can also be used to inhibit LH secretion in infertility protocols. In women, the GnRH analogs may cause hot flashes and sweating, as well as diminished libido, depression, and ovarian cysts. They are contraindicated in pregnancy and breastfeeding. In men, they initially cause a rise in testosterone that can result in bone pain. Hot flashes, edema, gynecomastia, and diminished libido may also occur.

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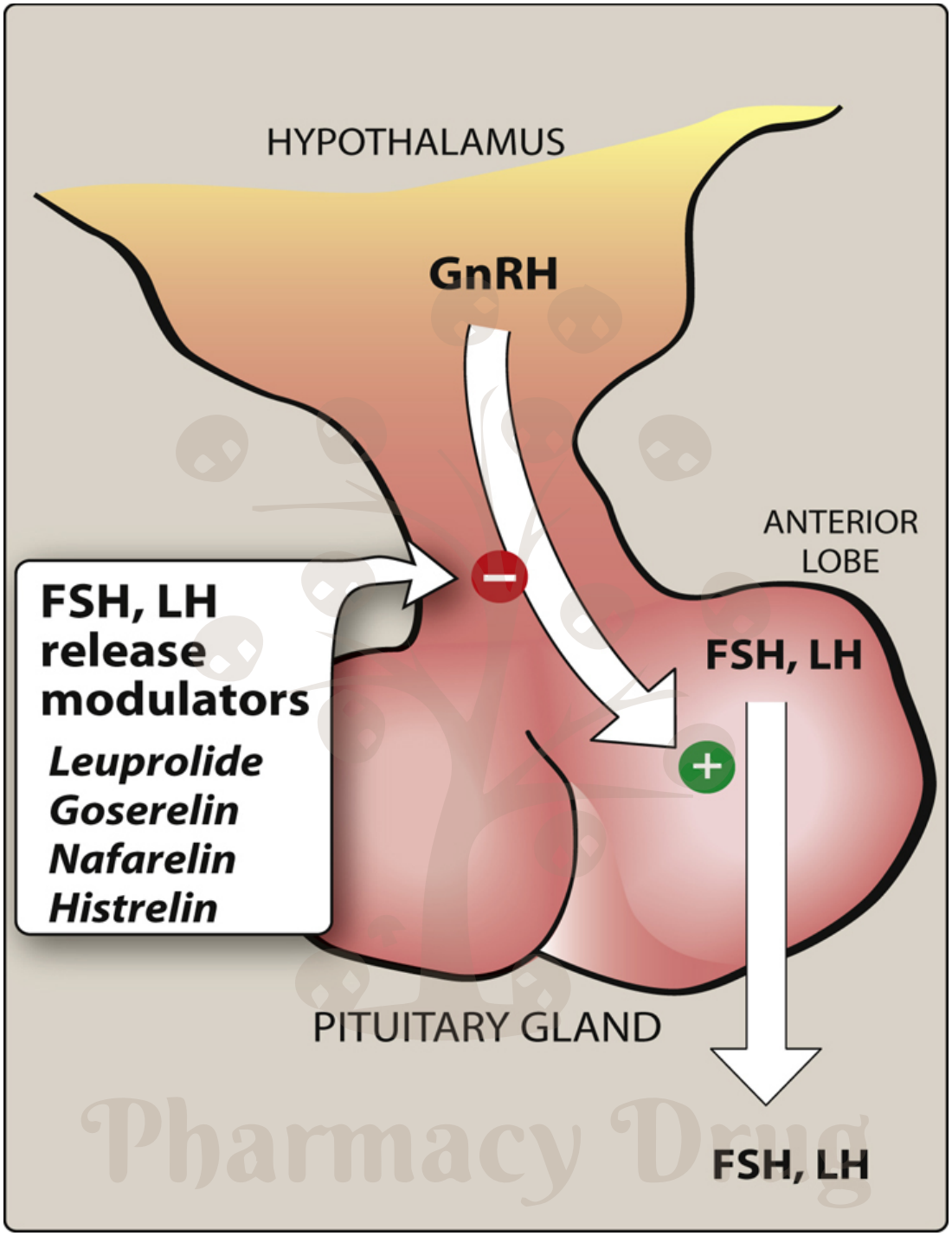

Figure 23.5 Secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH).GnRH = gonadotropin-releasing hormone.

E. Gonadotropins

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The gonadotropins (FSH and LH) are produced in the anterior pituitary. The regulation of gonadal steroid hormones depends on these agents. They find use in the treatment of infertility. *Menotropins* [men-oh-TROE-pinz] (also known as *human menopausal gonadotropins* or *hMG*) are obtained from urine of postmenopausal women and contain both FSH and LH. *Urofollitropin* [yoor-oh-fol-li-TROE-pin] is FSH obtained from postmenopausal women and is devoid of LH. *Follitropin* [fol-ih-TROE-pin] *alfa* and *follitropin beta* are FSH products manufactured using recombinant DNA technology. *Human chorionic gonadotropin* (*hCG*) is a placental hormone that is excreted in urine of pregnant women. The effects of *hCG* and *choriogonadotropin* [kore-ee-oh-goe-NAD-oh-troe-pin] *alfa* (made using recombinant DNA technology) are essentially identical to those of LH. All of these hormones are injected via the IM or subcutaneous route. In the treatment of infertility, injection of *hMG* or FSH products over a period of 5 to 12 days causes ovarian follicular growth and maturation, and with subsequent injection of *hCG*, ovulation occurs. Adverse effects include ovarian enlargement and possible ovarian hyperstimulation syndrome, which may be life threatening. Multiple births can occur.

F. Prolactin

Prolactin is a peptide hormone secreted by the anterior pituitary. Its primary function is to stimulate and maintain lactation. In addition, it decreases sexual drive and reproductive function. Thyrotropin-releasing hormone (TRH) stimulates the release of prolactin. Secretion is inhibited by dopamine acting at D_2 receptors (Figure 23.6). [Note: Drugs that act as dopamine antagonists (for example, *metoclopramide* and some antipsychotics) can increase the secretion of prolactin.] Hyperprolactinemia, which is associated with galactorrhea and hypogonadism, is treated with D_2 receptor agonists, such as *bromocriptine* and *cabergoline.* Both of these agents also find use in the treatment of pituitary microadenomas. [Note: *Bromocriptine*

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is also indicated for treatment of type 2 diabetes, although the effects on glucose are modest, and it is not a preferred agent (see Chapter 24).] Among their adverse effects are nausea, headache, and, less frequently, psychosis.

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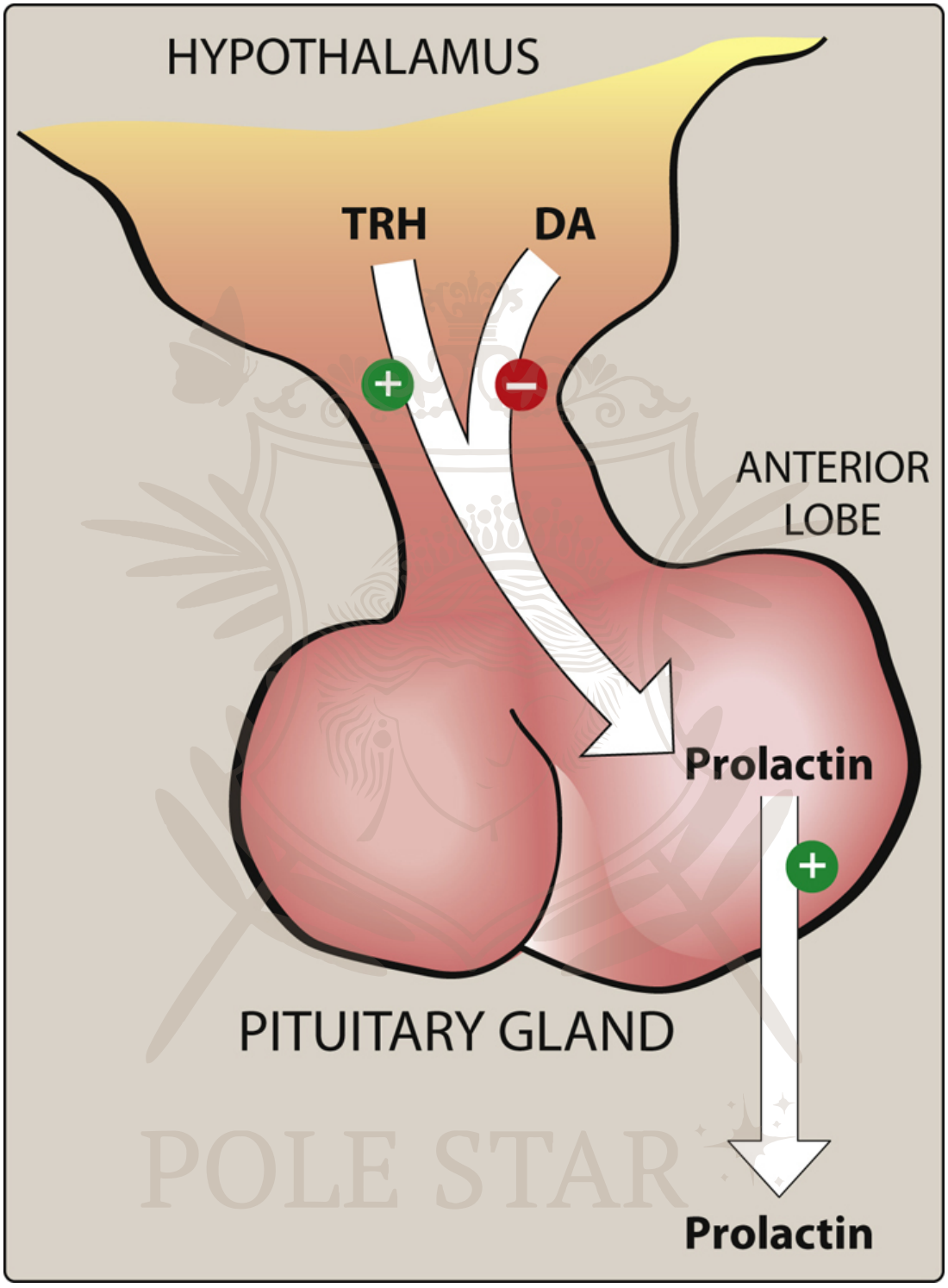

Figure 23.6 Secretion and action of prolactin.DA = dopamine; TRH = thyrotropin-releasing hormone.Adapted from R. R.Preston and T. E.Wilson . *Lippincott Illustrated Reviews*: Physiology. Philadelphia, PA, Lippincott Williams & Wilkins (2013).

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III. HORMONES OF THE POSTERIOR PITUITARY

In contrast to the hormones of the anterior lobe of the pituitary, those of the posterior lobe, *vasopressin* and *oxytocin*, are not regulated by releasing hormones. Instead, they are synthesized in the hypothalamus, transported to the posterior pituitary, and released in response to specific physiologic signals, such as high plasma osmolarity or parturition. Both hormones are administered intravenously and have very short half-lives. Their actions are summarized in Figure 23.7.

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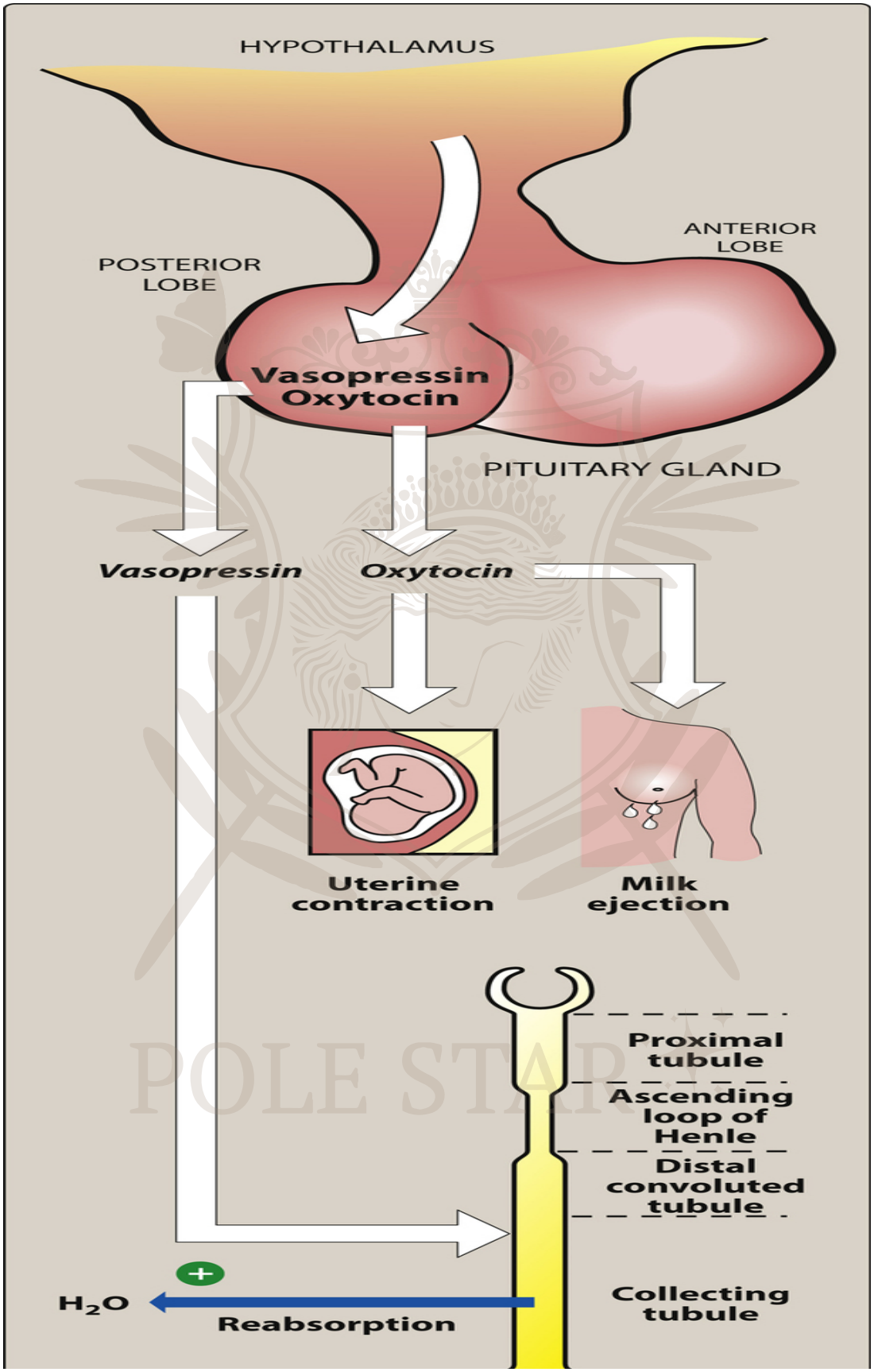

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Figure 23.7 Actions of *oxytocin* and *vasopressin*.

A. Oxytocin

Oxytocin is naturally produced during labor for childbirth, breastfeeding, and positive human contact. During breastfeeding, oxytocin causes milk ejection by contracting the myoepithelial cells around the mammary alveoli. Synthetic *oxytocin* [ok-se-TOE-sin] is used in obstetrics to stimulate uterine contraction and induce labor. Although toxicities are uncommon, hypertension, uterine rupture, water retention, and fetal death may occur. The antidiuretic and pressor activities of *oxytocin* are much less than those of *vasopressin*.

B. Vasopressin

Vasopressin [vas-oh-PRESS-in] (antidiuretic hormone) is structurally related to *oxytocin* (different by only two amino acids). This neuropeptide hormone, synthesized in the hypothalamus and secreted from the posterior pituitary gland, has both antidiuretic and vasopressor effects (Figure 23.7). In the kidney, it binds to the V_2 receptor to increase water permeability, driving reabsorption in the collecting tubules. Thus, the major use of *vasopressin* is to treat diabetes insipidus, where it results in a decrease in urine formation. It also finds use in septic shock and in controlling bleeding due to esophageal varices. Other effects of *vasopressin* are mediated by the V_1 receptor, which is found in the liver, vascular smooth muscle (where it causes constriction), and other tissues. The major toxicities of *vasopressin* are water intoxication and hyponatremia. Abdominal pain, tremor, and vertigo can also occur. *Desmopressin* [des-moe-PRESS-in], an analog of *vasopressin*, has minimal activity at the V_1 receptor, making it largely free of pressor effects. This analog is longer acting than *vasopressin*, and since it acts as a selective agonist of V_2 receptors, is preferred for the treatment of diabetes insipidus and

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nocturnal enuresis. For these indications, *desmopressin* is given by intranasal or oral routes of administration. [Note: The nasal spray should not be used for enuresis due to reports of seizures in children using this formulation.] Local irritation may occur with the nasal spray.

IV. THYROID HORMONES

The thyroid gland facilitates normal growth and maturation by maintaining a level of metabolism in the tissues that is optimal for normal function. The two major thyroid hormones are triiodothyronine (T_3; most active form) and thyroxine (T_4; most abundant form). Inadequate secretion of thyroid hormone (hypothyroidism) results in a slowing of metabolic processes. Hypothyroidism may manifest as many different symptoms, including bradycardia, cold intolerance, weight gain, fatigue, and mental impairment. In children, hypothyroidism can cause intellectual impairment and dwarfism. By contrast, excess secretion of thyroid hormones (hyperthyroidism) can cause tachycardia, cardiac arrhythmias, body wasting, nervousness, tremor, and heat intolerance.

A. Thyroid hormone synthesis and secretion

The thyroid gland is made up of multiple follicles that consist of a single layer of epithelial cells surrounding a lumen filled with thyroglobulin (the storage form of thyroid hormone). Thyroid function is controlled by TSH (thyrotropin), which is synthesized by the anterior pituitary (Figure 23.8). [Note: The hypothalamic TRH governs the generation of TSH.] TSH action is mediated by cAMP and leads to stimulation of iodide (I^-) uptake by the thyroid gland. Oxidation to iodine (I_2) by a peroxidase is followed by iodination of tyrosines on thyroglobulin. [Note: Antibodies to thyroid peroxidase are diagnostic for Hashimoto thyroiditis, a common cause of hypothyroidism.] Condensation of two diiodotyrosine residues gives rise to T_4, whereas condensation of

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a monoiodotyrosine residue with a diiodotyrosine residue generates T_3. The hormones are released following proteolytic cleavage of the thyroglobulin. A summary of the steps in thyroid hormone synthesis and secretion is shown in Figure 23.9.

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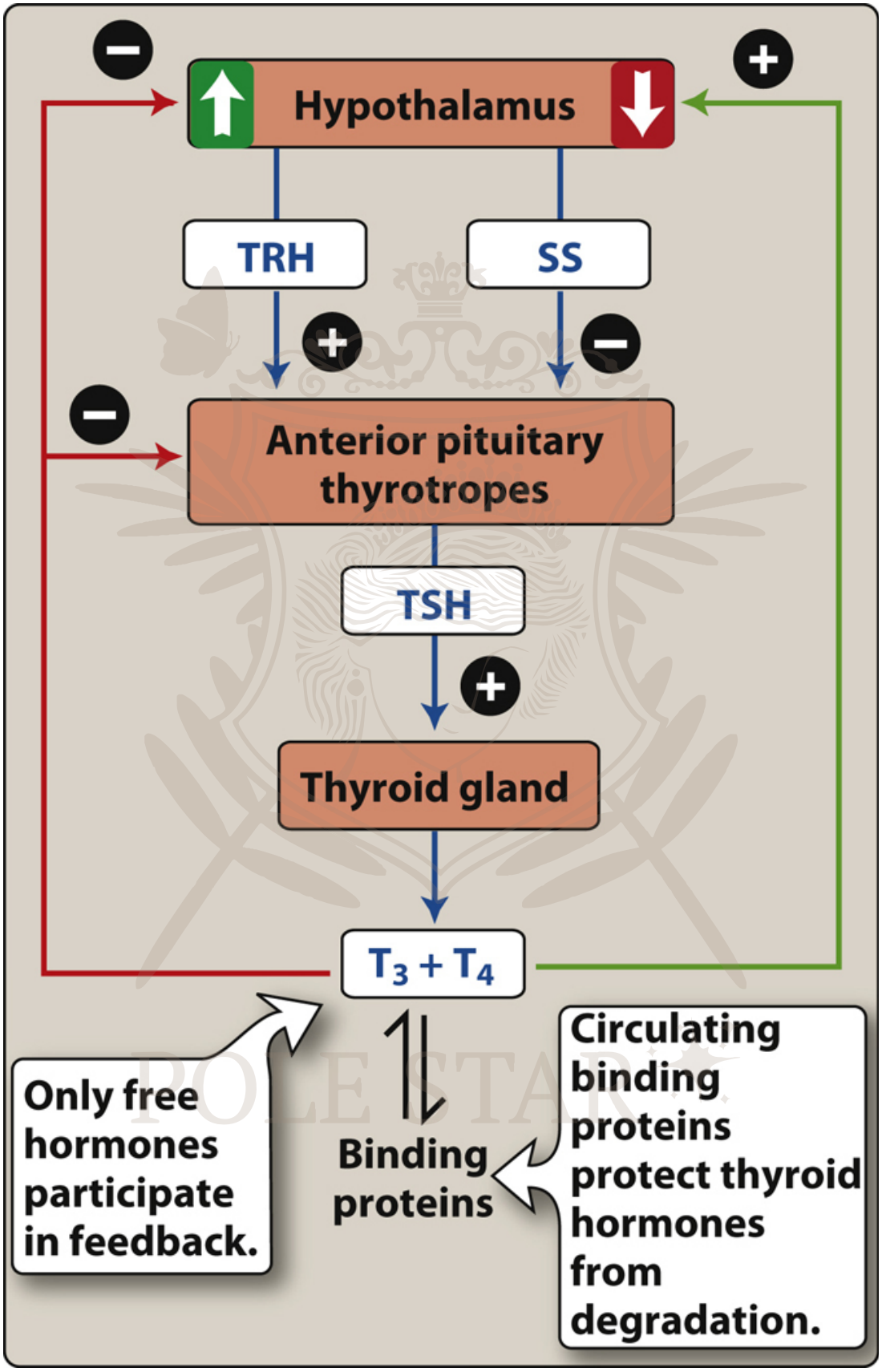
Hypothalamus
TRH
SS
Anterior pituitary thyrotropes
TSH
Thyroid gland
$T_3 + T_4$
Binding proteins
Only free hormones participate in feedback.
Circulating binding proteins protect thyroid hormones from degradation.

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Figure 23.8 Feedback regulation of thyroid hormone release.SS = somatostatin; T_3 = triiodothyronine; T_4 = thyroxine; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone.

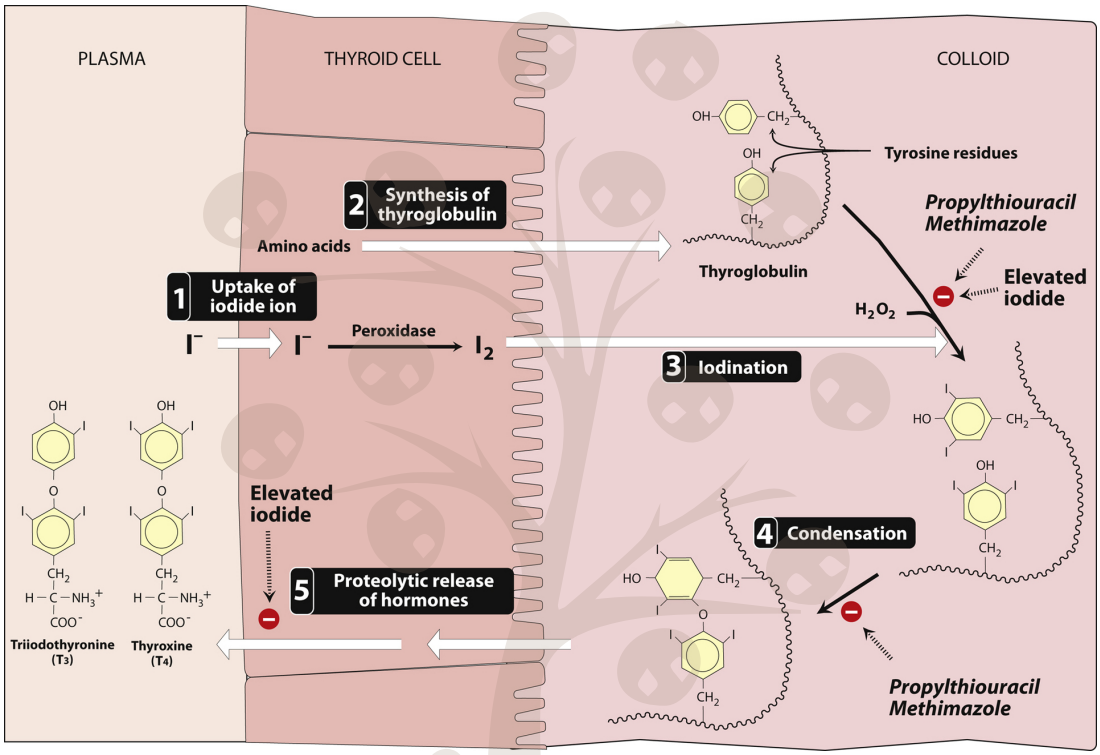

Figure 23.9 Biosynthesis of thyroid hormones.

B. Mechanism of action

Most circulating T_3 and T_4 is bound to thyroxine-binding globulin, the protein responsible for transporting thyroid hormones in the plasma. The hormones must dissociate from thyroxine-binding globulin prior to entry into cells. In the cell, T_4 is enzymatically deiodinated to T_3, which enters the nucleus and attaches to specific receptors. The activation of these receptors promotes the stimulation of oxygen consumption, mitochondrial genome expression, and mitochondriogenesis.

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C. Pharmacokinetics

Both T_4 and T_3 are absorbed after oral administration; however, food, calcium preparations, iron salts, and aluminum-containing antacids can decrease the absorption of both. Deiodination is the major route of metabolism of T_4, which is converted to active or inactive forms of T_3. T_3 also undergoes sequential deiodination as an inactivating pathway. The hormones are also metabolized via conjugation with glucuronides and sulfates that are excreted and cleared via bile or urinary pathways.

D. Treatment of hypothyroidism

Hypothyroidism usually results from autoimmune destruction of the gland and is diagnosed by elevated TSH. *Levothyroxine* (T_4) [leh-vo-thye-ROK-sin] is preferred over T_3 (*liothyronine* [lye-oh-THYE-roe-neen]) or T_3/T_4 combination products (*liotrix* [LYE-oh-trix]) for the treatment of hypothyroidism. *Levothyroxine* is better tolerated than T_3 preparations and has a longer half-life. It is dosed once daily and steady state is achieved in 6 to 8 weeks. Symptoms generally improve within a few weeks, although complete recovery may take months. Goals of therapy include a normalization of TSH and an improvement in symptoms. If the dosage of thyroid medication is too great, toxicity mirrors the symptoms of hyperthyroidism. Toxicity is directly related to both T_3/T_4 levels and manifests as nervousness, palpitations and tachycardia, heat intolerance, and unexplained weight loss. Drugs that induce the cytochrome P-450 enzymes, such as *phenytoin*, *rifampin*, and *phenobarbital*, accelerate metabolism of thyroid hormones and may decrease the effectiveness (Figure 23.10).

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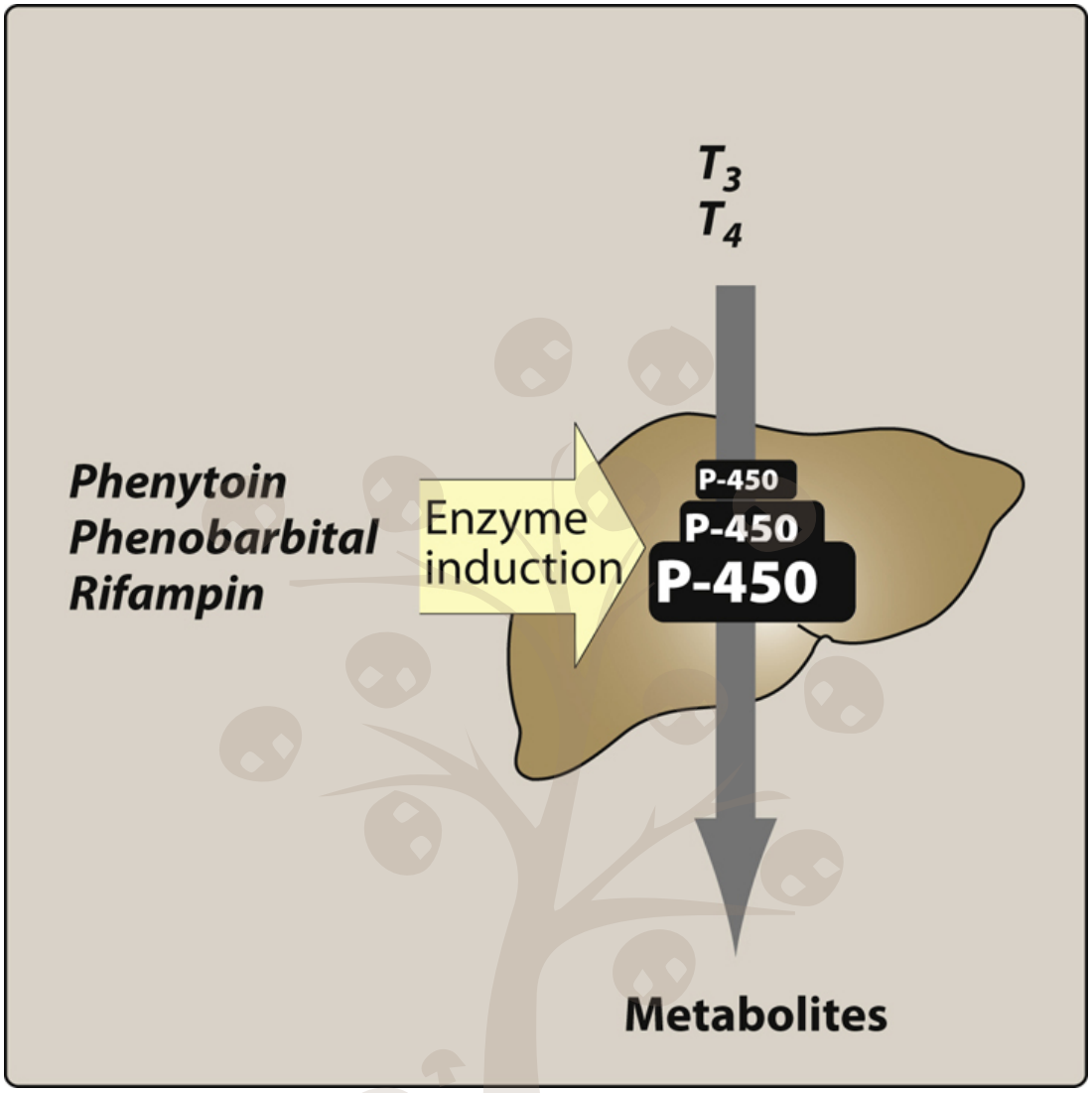

Figure 23.10 Enzyme induction can increase the metabolism of the thyroid hormones.T_3 = triiodothyronine; T_4 = thyroxine.

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E. Treatment of hyperthyroidism (thyrotoxicosis)

Graves disease, an autoimmune disease that affects the thyroid, is the most common cause of hyperthyroidism. In these situations, TSH levels are low due to negative feedback. [Note: Feedback inhibition of TRH occurs with high levels of circulating thyroid hormone, which, in turn, decreases secretion of TSH.] The goal of therapy is to decrease synthesis and/or release of additional

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hormone. This can be accomplished by removing part or all of the thyroid gland, by inhibiting synthesis of the hormones, or by blocking release of hormones from the follicle.

1. **Inhibition of thyroid function:** Inhibition of the thyroid can be accomplished surgically or by destruction of the gland with radioactive iodine (^{131}I), which is selectively taken up by the thyroid follicular cells. Most patients develop hypothyroidism after treatment with radioactive iodine and require treatment with *levothyroxine*.

2. **Inhibition of thyroid hormone synthesis:** The thioamides, *propylthiouracil* [proe-pil-thye-oh-YOOR-ah-sil] (*PTU*) and *methimazole* [me-THIM-ah-zole], inhibit both the oxidative processes required for iodination of tyrosyl groups and the condensation (coupling) of iodotyrosines to form T_3 and T_4 (Figure 23.9). *PTU* also blocks the peripheral conversion of T_4 to T_3. [Note: These drugs have no effect on thyroglobulin already stored in the gland. Therefore, clinical effects may be delayed until thyroglobulin stores are depleted (Figure 23.11).] Adverse effects of thioamide therapy may include rash, pruritis, and arthralgia. Both agents have been associated with agranulocytosis and hepatoxicity, although *PTU* has been associated with more severe forms of liver injury, including potentially fatal acute liver failure. *Methimazole* is preferred over *PTU* because it has a longer half-life, allowing for once-daily dosing, and a lower incidence of adverse effects. However, *PTU* is recommended during the first trimester of pregnancy due to a greater risk of teratogenic effects with *methimazole*.

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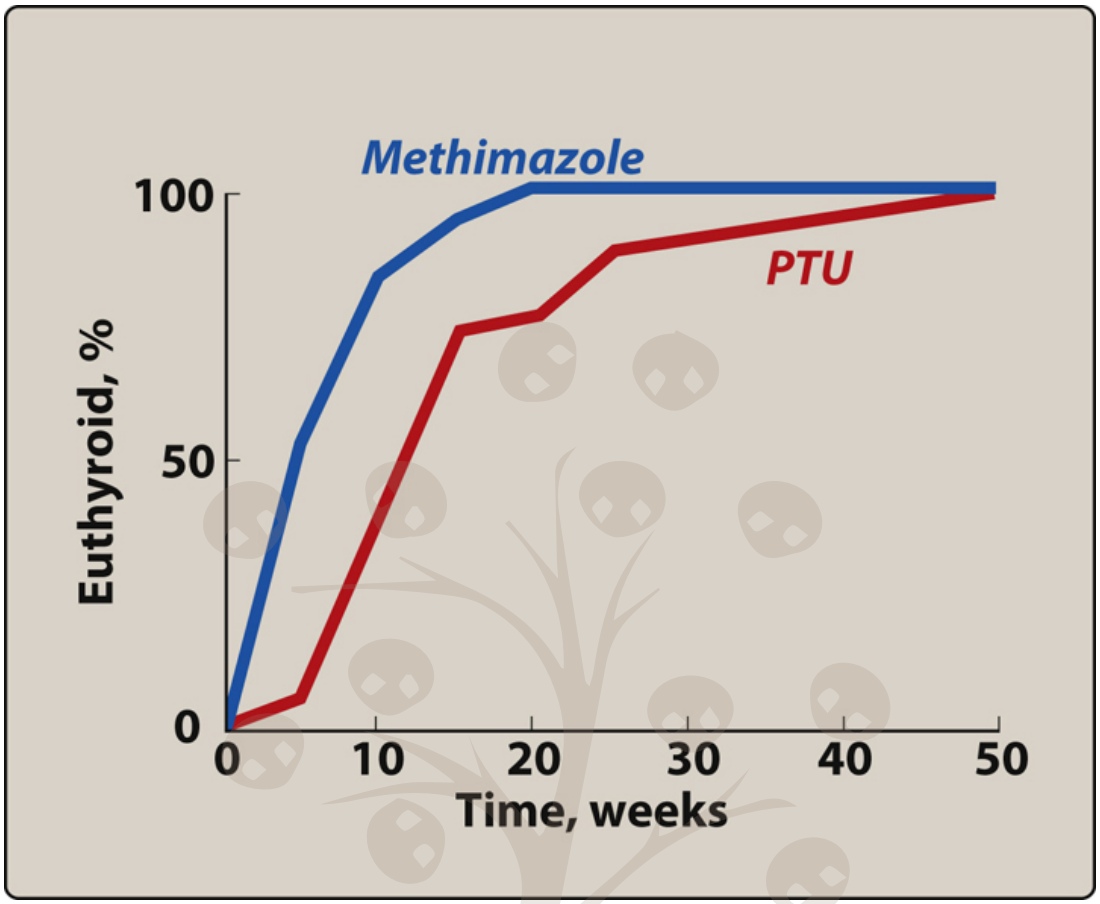

Figure 23.11 Time required for patients with Graves hyperthyroidism to become euthyroid with normal serum T_4 and T_3 concentrations.Modified from K.Okamura , H.Ikenoue , and A.Shiroozu . Reevaluation of the effects of methylmercaptoimidazole and propylthiouracil in patients with Graves' hyperthyroidism. *J. Clin. Endocrinol. Metab*. 65: 719 (1987).

3.Blockade of hormone release: A pharmacologic dose of *iodide* inhibits the iodination of tyrosines ("Wolff–Chaikoff effect"), but this effect lasts only a few days. More importantly, *iodide* inhibits the release of thyroid hormones from thyroglobulin by mechanisms not yet understood. *Iodide* is employed to treat thyroid storm or prior to surgery, because it decreases the vascularity of the thyroid gland. *Iodide*, administered orally, is not useful for long-term therapy. Adverse effects include sore mouth and throat, swelling of the

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tongue or larynx, rashes, ulcerations of mucous membranes, and metallic taste.

4. Thyroid storm: Thyroid storm presents with extreme symptoms of hyperthyroidism. The treatment of thyroid storm is the same as for hyperthyroidism, except that the drugs are given in higher doses and more frequently. β-Blockers, such as *metoprolol, atenolol,* or *propranolol*, are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism.

Clinical Application 23.2: Management of Hypo- and Hyperthyroidism

Thyroid function is evaluated by laboratory monitoring of TSH. If the TSH is elevated, hypothyroidism may be present. When TSH is decreased, hyperthyroidism may be suspected. In either case, additional tests are indicated to confirm the diagnosis and assess the impact on metabolic systems. Hypothyroidism results most commonly when the thyroid gland is not able to produce enough thyroid hormone, and the disorder can result in decreased heart rate, intolerance to cold temperatures, slow metabolism, and weight gain. Synthetic preparations of T_4 (*levothyroxine*) are preferred for the management of hypothyroidism. Effectiveness of treatment is assessed through monitoring of TSH and improvement in symptoms of hypothyroidism. Due to the long half-life of T_4 (7-10 days), improvement in symptoms often takes weeks, and the TSH should be measured 6 to 8 weeks after initiation or a dosage change to determine the full impact of treatment.

Hyperthyroidism occurs when there is too much thyroid hormone present, and the disorder results in increased metabolism with symptoms associated with the heart (palpitations, tachycardia), heat intolerance, weight loss, and mood disturbance. The timeline for improvement in symptoms of hyperthyroidism is based on the therapy selected. Thioamides (*methimazole*, *propylthiouracil*) can produce a euthyroid state in as little as 3 to 8 weeks. Radioactive iodine may take several months to destroy overactive tissue in the thyroid gland. Surgery is an option for patients with severe hyperthyroidism who require more immediate effects.

Chapter Summary

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- The pituitary gland, commonly referred to as the “master gland,” produces hormones that regulate various processes and functions throughout the body.
- Adrenocorticotropic hormone (ACTH) is released by the pituitary and controls the response to stress.
- Somatotropin, also referred to as growth hormone (GH), drives processes of cell proliferation and bone growth. *Somatropin* (synthetic growth hormone) is used in the treatment of GH deficiency, growth failure in children, treatment of HIV patients with cachexia, and GH replacement in adults with confirmed deficiency.
- Somatostatin (growth hormone–inhibiting hormone) inhibits release of GH, insulin, glucagon, and gastrin. *Octreotide* and *lanreotide* are synthetic analogs of somatostatin used in the treatment of acromegaly and in severe diarrhea/flushing episodes associated with carcinoid tumors. *Octreotide* may also be used for the treatment of bleeding esophageal varices.
- Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are gonadotropins and regulate essential roles in reproduction.
- Continuous administration of gonadotropin releasing hormone (GnRH) analogs, such as *leuprolide*, is effective in suppressing production of FSH and LH, which leads to reduced production of androgens and estrogens. These agents are effective in the treatment of prostate cancer, endometriosis, and precocious puberty. They can also be used to suppress the LH surge and prevent premature ovulation in women undergoing controlled ovarian stimulation protocols for the treatment of infertility.
- The posterior pituitary hormones, *vasopressin* and *oxytocin*, are not regulated but synthesized in the hypothalamus and released in response to physiologic signals. *Oxytocin* is used in obstetrics to stimulate uterine contraction and induce labor. *Vasopressin* is used to treat diabetes insipidus. It may also be used in septic shock and in controlling bleeding due to esophageal varices. *Desmopressin* is an analog of *vasopressin* that is preferred for the treatment of diabetes insipidus and nocturnal enuresis.
- The thyroid gland regulates the metabolic processes in the body, with negative feedback driven by T_3 and T_4 hormones.
- Symptoms of hypothyroidism may include bradycardia, cold intolerance, weight gain, fatigue, and mental impairment. *Levothyroxine* (T_4) is preferred over T_3 (*liothyronine*) or T_3/T_4 combination products for the treatment of hypothyroidism.
- Symptoms of hyperthyroidism may include tachycardia, cardiac arrhythmias, body wasting, nervousness, tremor, and heat intolerance. Treatment may involve removing part or all of the thyroid gland (surgery or *radioactive iodine* (^{131}I)), inhibiting synthesis of the hormones

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(*methimazole* or *propylthiouracil*), or blocking release of hormones from the follicle *(iodide).*

STUDY QUESTIONS

Choose the ONE best answer.

23.1 Which of the following hormones is correctly matched with its primary effect?

A. Prolactin—promotes growth of body tissues
B. FSH—stimulates ovarian follicle growth
C. TSH—regulates sleep cycles
D. Oxytocin—increases glucose levels

Correct answer = B. FSH. See Figure 23.2. FSH stimulates ovarian follicle growth and may be used in infertility. Prolactin stimulates and maintains lactation. TSH regulates thyroid function. Oxytocin stimulates uterine contractions and induces labor.

23.2 Which of the following agents is correctly paired with an appropriate clinical use of the drug?

A. Desmopressin—treatment of diabetes insipidus
B. Goserelin—growth hormone deficiency
C. hCG—treatment of bleeding esophageal varices
D. Octreotide—treatment of infertility

Correct answer = A. Goserelin is a GnRH analog that is used for the treatment of prostate cancer or endometriosis. HCG is used in the treatment of infertility. Octreotide is used in the treatment of bleeding esophageal varices.

23.3 A 31-year-old man presents to his endocrinologist for the management of a new diagnosis of acromegaly. Which of the following drugs would be most beneficial in the treatment of this patient?

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A. Cosyntropin
B. Lanreotide
C. Oxytocin
D. Somatropin

Correct answer = B. Lanreotide is a synthetic analog of somatostatin, which inhibits GH. Acromegaly is characterized by an excess of GH. Cosyntropin is used as a diagnostic tool in adrenal insufficiency. Oxytocin is used for induction of labor. Somatropin is synthetic human GH, so it would not be beneficial.

23.4 A 40-year-old woman is undergoing infertility treatments. Which of the following drugs is most likely to be included in her treatment regimen?

A. Cabergoline
B. Follitropin
C. Methimazole
D. Vasopressin

Correct answer = B. Follitropin is a recombinant version of FSH that causes ovarian follicular growth and maturation. Cabergoline is a dopamine agonist that is used for hyperprolactinemia. Methimazole is the treatment of choice for hyperthyroidism. Vasopressin is an antidiuretic hormone.

23.5 A 51-year-old woman with human immunodeficiency virus (HIV) infection complains of involuntary weight loss and weakness for the past month. Which of the following agents could be prescribed for the treatment of the patient's HIV-related cachexia?

A. Somatropin
B. Leuprolide
C. Menotropin
D. Corticotropin

Correct answer = A. Somatropin is used in the treatment of GH deficiency, growth failure in children, treatment of HIV-associated cachexia, and GH

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replacement in adults with confirmed deficiency. Leuprolide, menotropins, and corticotropin are not indicated for management of cachexia.

23.6 A 29-year-old woman with complaints of fatigue and weight gain presents for her annual physical exam. Her TSH is 13.5 mIU/L (normal 0.5-4.7 mIU/L). Which of the following agents is most appropriate to treat the TSH abnormality?

A. Levothyroxine
B. Liothyronine
C. Liotrix
D. Propylthiouracil

Correct answer = A. This patient presents with hypothyroidism as evidenced by high TSH. Levothyroxine is preferred due to its long half-life and better tolerability. Liothyronine (T_3) and liotrix (T_3/T_4) are not as well tolerated. Propylthiouracil is used in the treatment of hyperthyroidism.

23.7 A 45-year-old woman requires levothyroxine for a new diagnosis of hypothyroidism. Her current medications include metoprolol and pravastatin. She also takes calcium carbonate and vitamin D supplements. Which of her medications may affect the levothyroxine dosage requirements?

A. Pravastatin
B. Calcium carbonate
C. Metoprolol
D. Vitamin D

Correct answer = B. Calcium carbonate may reduce the absorption of levothyroxine. The other medications should not interact with the levothyroxine. Administration of levothyroxine and calcium should be separated by at least 4 hours.

23.8 Which of the following symptoms indicates that a patient may need a lower dosage of levothyroxine?

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A. Bradycardia
B. Cold intolerance
C. Palpitations
D. Weight gain

Correct answer = C. Palpitations are an adverse effect of too much thyroid supplementation. The other symptoms are indicative of untreated or undertreated hypothyroidism and may require an increase in thyroid supplementation.

23.9 A 26-year-old woman presents with complaints of irritability, tremor, and heart palpitations. A laboratory evaluation reveals a low TSH and high free T_4 concentration. She is currently in her first trimester of pregnancy. Which of the following treatments option is most appropriate for this patient?

A. Methimazole
B. Propylthiouracil
C. Radioactive iodine
D. Surgical removal of the thyroid

Correct answer = B. Methimazole is generally preferred over PTU for the treatment of hyperthyroidism because it has a longer half-life and lower incidence of adverse effects. However, PTU is recommended in the first trimester of pregnancy due to a greater risk of teratogenic effects with methimazole. Surgery is not ideal in a pregnant patient. Radioactive iodine is contraindicated due to potential effects on the fetus.

23.10 A 24-year-old patient is given iodide to decrease the vascularity of the thyroid gland prior to surgery. What adverse effect is the patient most likely to experience?

A. Sore throat
B. Fatigue
C. Heart palpitations
D. Headache

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Correct answer = A. Adverse effects of iodide may include sore mouth and throat, swelling of the tongue or larynx, rashes, ulcerations of mucous membranes, and metallic taste.

POLE STAR

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24

Drugs for Diabetes

Karen L. Whalen, Lihui Yuan

I. OVERVIEW

The pancreas produces the peptide hormones insulin, glucagon, and somatostatin. The peptide hormones are secreted from cells in the islets of Langerhans (β cells produce insulin, α cells produce glucagon, and δ cells produce somatostatin). These hormones play an important role in regulating metabolic activities of the body, particularly glucose homeostasis. A relative or absolute lack of insulin, as seen in diabetes mellitus, can cause serious hyperglycemia. Left untreated, complications such as retinopathy, nephropathy, neuropathy, and atherosclerotic cardiovascular disease (ASCVD) may result. Administration of insulin preparations or other glucose-lowering agents (Figure 24.1) can reduce morbidity and mortality associated with diabetes.

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INSULIN AND INSULIN ANALOGS

Inhaled insulin AFREZZA
Insulin aspart FIASP, NOVOLOG
Insulin degludec TRESIBA
Insulin detemir LEVEMIR
Insulin glargine BASAGLAR, LANTUS, SEMGLEE, TOUJEO
Insulin glulisine APIDRA
Insulin lispro ADMELOG, HUMALOG, LYUMJEV
NPH insulin suspension HUMULIN N, NOVOLIN N
Regular insulin HUMULIN R, NOVOLIN R

AMYLIN ANALOG

Pramlintide SYMLIN

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GLP-1 RECEPTOR AGONISTS

Dulaglutide TRULICITY
Exenatide BYETTA, BYDUREON
Liraglutide VICTOZA
Lixisenatide ADLYXIN
Semaglutide OZEMPIC, RYBELSUS

BIGUANIDES

Metformin GLUMETZA, RIOMET

SULFONYLUREAS

Glimepiride AMARYL
Glipizide GLUCOTROL
Glyburide DIABETA, GLYNASE

MEGLITINIDES

Nateglinide GENERIC ONLY
Repaglinide GENERIC ONLY

THIAZOLIDINEDIONES

Pioglitazone ACTOS
Rosiglitazone AVANDIA

DPP-4 INHIBITORS

Alogliptin NESINA
Linagliptin TRADJENTA
Saxagliptin ONGLYZA
Sitagliptin JANUVIA

SGLT2 INHIBITORS

Canagliflozin INVOKANA
Dapagliflozin FARXIGA
Empagliflozin JARDIANCE
Ertugliflozin STEGLATRO

α-GLUCOSIDASE INHIBITORS

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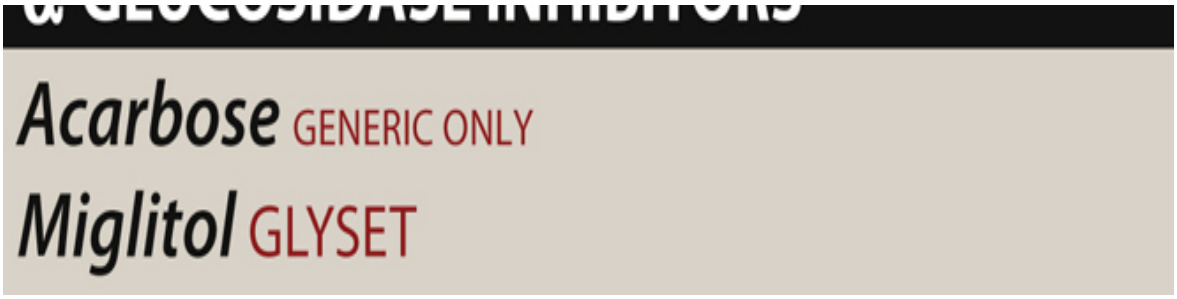

Figure 24.1 Summary of drugs used in the treatment of diabetes.GLP-1 = glucagon-like peptide-1; DPP-4 = dipeptidyl peptidase-4; SGLT2 = sodium–glucose cotransporter 2.

II. DIABETES MELLITUS

The incidence of diabetes is growing rapidly in the United States and worldwide. An estimated 34.2 million people in the United States and 463 million people worldwide are afflicted with diabetes. Diabetes is not a single disease. Rather, it is a heterogeneous group of syndromes characterized by elevated blood glucose attributed to a relative or absolute deficiency of insulin. The American Diabetes Association (ADA) recognizes four clinical classifications of diabetes: type 1 diabetes, type 2 diabetes, gestational diabetes, and diabetes due to other causes such as genetic defects, pancreatic disorders, or medications. Figure 24.2 summarizes the characteristics of type 1 and type 2 diabetes. Gestational diabetes is defined as diabetes diagnosed in the second or third trimester of pregnancy in women who did not have known diabetes prior to gestation.

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	Type 1	Type 2
Age at onset	Usually during childhood or puberty	Commonly over age 35
Nutritional status at time of onset	Commonly undernourished	Obesity usually present
Prevalence among diagnosed diabetics	5%-10%	90%-95%
Genetic predisposition	Moderate	Very strong
Defect or deficiency	β Cells are destroyed, eliminating the production of insulin	Inability of β cells to produce appropriate quantities of insulin; insulin resistance; other defects

Figure 24.2 Comparison of type 1 and type 2 diabetes.

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Clinical Application 24.1 Diagnosis of Diabetes

Diabetes is diagnosed using glucose or glycosylated hemoglobin values. According to the American Diabetes Association, a fasting plasma glucose of ≥126 mg/dL (7.0 mmol/L) or a 2-hour postprandial glucose ≥200 mg/dL (11.1 mmol/L) is consistent with a diagnosis of diabetes. Glycosylated hemoglobin (A1C) is a marker of overall glucose control. The rate of formation of A1C is proportional to the average blood glucose concentration over the previous 3 months. An A1C value ≥6.5% is consistent with a diagnosis of diabetes. If the patient has an elevated fasting glucose, postprandial glucose, or A1C but does not have overt signs of hyperglycemia (for example, polyuria, polydipsia, or polyphagia), repeat testing (on the same or another sample) should be performed as soon as possible to confirm the diagnosis of diabetes. [Note: Patients with borderline elevated fasting glucose (100-125 mg/dL), postprandial glucose (140-199 mg/dL), or A1C 5.7% to 6.4% are considered to have prediabetes.]

A. Type 1 diabetes

Type 1 diabetes most commonly afflicts children, adolescents, or young adults, but some latent forms occur later in life. The disease is characterized by an absolute deficiency of insulin due to destruction of β cells. Without functional β cells, the pancreas fails to respond to glucose, and a person with type 1 diabetes shows classic symptoms of insulin deficiency, such as polydipsia, polyphagia, polyuria, and weight loss.

1.Cause: Loss of β-cell function in type 1 diabetes results from autoimmune-mediated processes that may be triggered by viruses or other environmental toxins. In patients without diabetes, constant β-cell secretion maintains low basal levels of circulating insulin. This suppresses lipolysis, proteolysis, and glycogenolysis. A burst of insulin secretion occurs within 2 minutes after ingesting a meal, in response to transient increases in circulating glucose and amino acids. This lasts for up to 15 minutes, followed by the postprandial secretion of insulin. However, without functional β cells, those with type 1 diabetes can neither maintain basal secretion of insulin nor release a bolus of insulin to respond to variations in circulating glucose (Figure 24.3).

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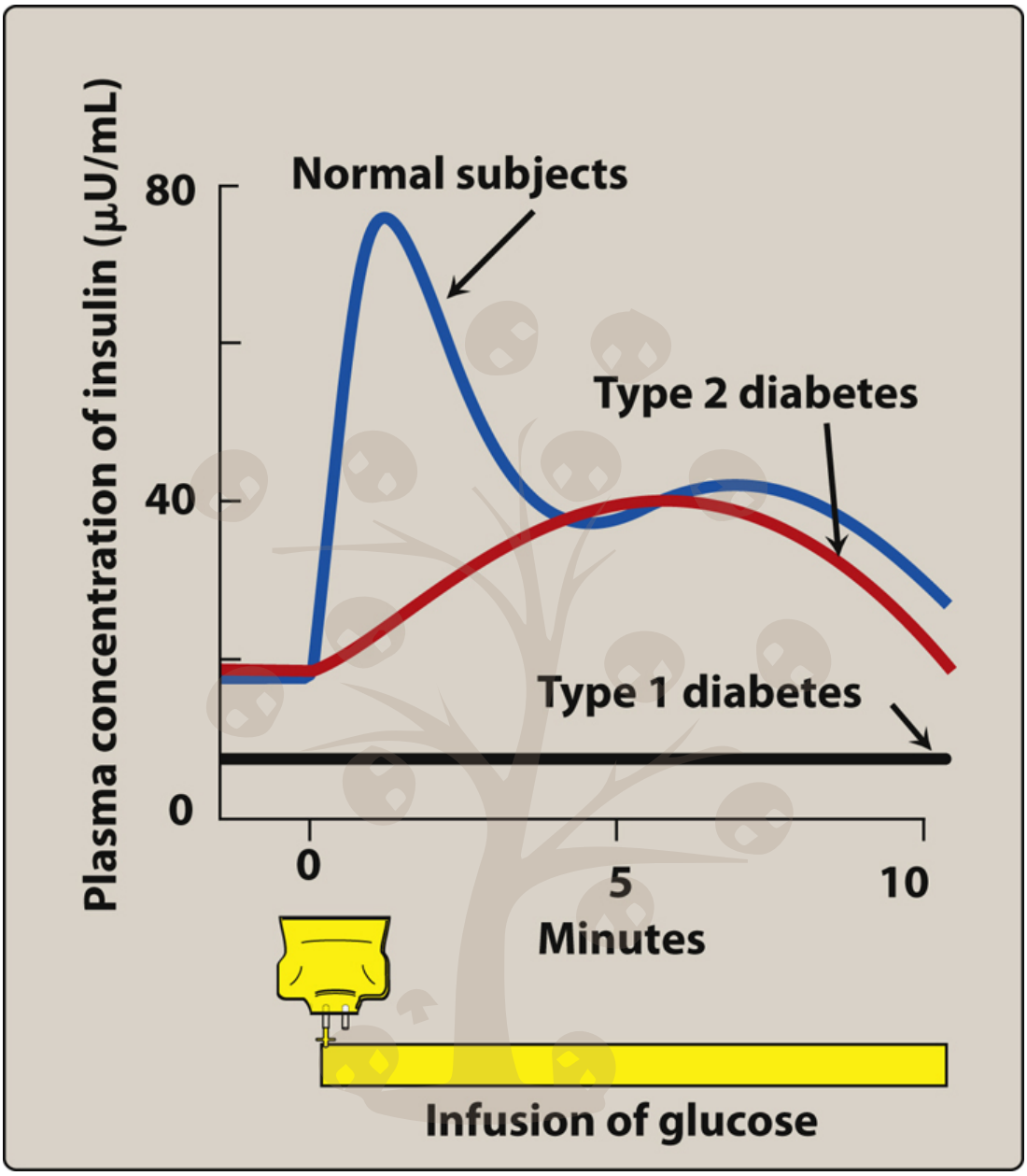

Figure 24.3 Release of insulin that occurs in response to an IV glucose load in normal subjects and patients with diabetes.

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2.Treatment: Patients with type 1 diabetes must rely on exogenous insulin to control hyperglycemia, avoid ketoacidosis, and maintain acceptable levels of glycosylated hemoglobin (A1C). [Note: A1C is a marker of overall glucose control and is used to monitor diabetes in clinical practice. The rate of formation of A1C is proportional to the average blood glucose concentration over the

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previous 3 months. A higher average glucose results in a higher A1C.] The goal of insulin therapy in type 1 diabetes is to maintain blood glucose as close to normal as possible and to avoid wide fluctuations in glucose. The use of home blood glucose monitors and continuous glucose monitors facilitates frequent self-monitoring and treatment with insulin.

Clinical Application 24.2 Glycemic Targets in the Management of Diabetes

Optimal glycemic control reduces the risk of long-term complications of diabetes, such as nephropathy, neuropathy, and retinopathy, as well as the risk of short-term complications such as hypoglycemia and hyperglycemic crisis. The recommended range for fasting plasma glucose in the management of diabetes is 80 to 130 mg/dL and that for postprandial glucose is less than 180 mg/dL. Goals are more stringent in patients with gestational diabetes (for example, fasting plasma glucose 70-95 mg/dL). The recommended A1C goal for most patients with diabetes is less than 7%. Goals may be less stringent in elderly patients or those with multiple coexisting illnesses or limited life expectancy (for example, A1C less than 8%) and more stringent in gestational diabetes (for example, A1C less than 6% if this can be obtained without significant hypoglycemia). [Note: The A1C value provides a marker of estimated average glucose (eAG) over the last 3 months. The relationship of A1C to eAG is illustrated by the formula: eAG = 28.7 × A1C – 46.7. For instance, an A1C of 7% provides an eAG of 154 mg/dL (28.7 × 7-46.7 = 154).]

B. Type 2 diabetes

Type 2 diabetes accounts for greater than 90% of cases. Type 2 diabetes is influenced by genetic factors, aging, obesity, and peripheral insulin resistance, rather than autoimmune processes. The metabolic alterations are generally milder than those observed with type 1 diabetes (for example, patients with type 2 diabetes typically are not ketotic), but the long-term clinical consequences are similar if-diabetes is not controlled.

1.Cause: Type 2 diabetes is characterized by a lack of sensitivity of target organs to insulin (Figure 24.4). In type 2 diabetes, the pancreas retains some β-cell function, but insulin secretion is insufficient to maintain glucose homeostasis (Figure 24.3) in the face of increasing peripheral insulin resistance. The β-cell mass

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may gradually decline over time in type 2 diabetes. In contrast to patients with type 1 diabetes, those with type 2 diabetes are often overweight or obese. Obesity contributes to insulin resistance, which is considered the major underlying defect of type 2 diabetes.

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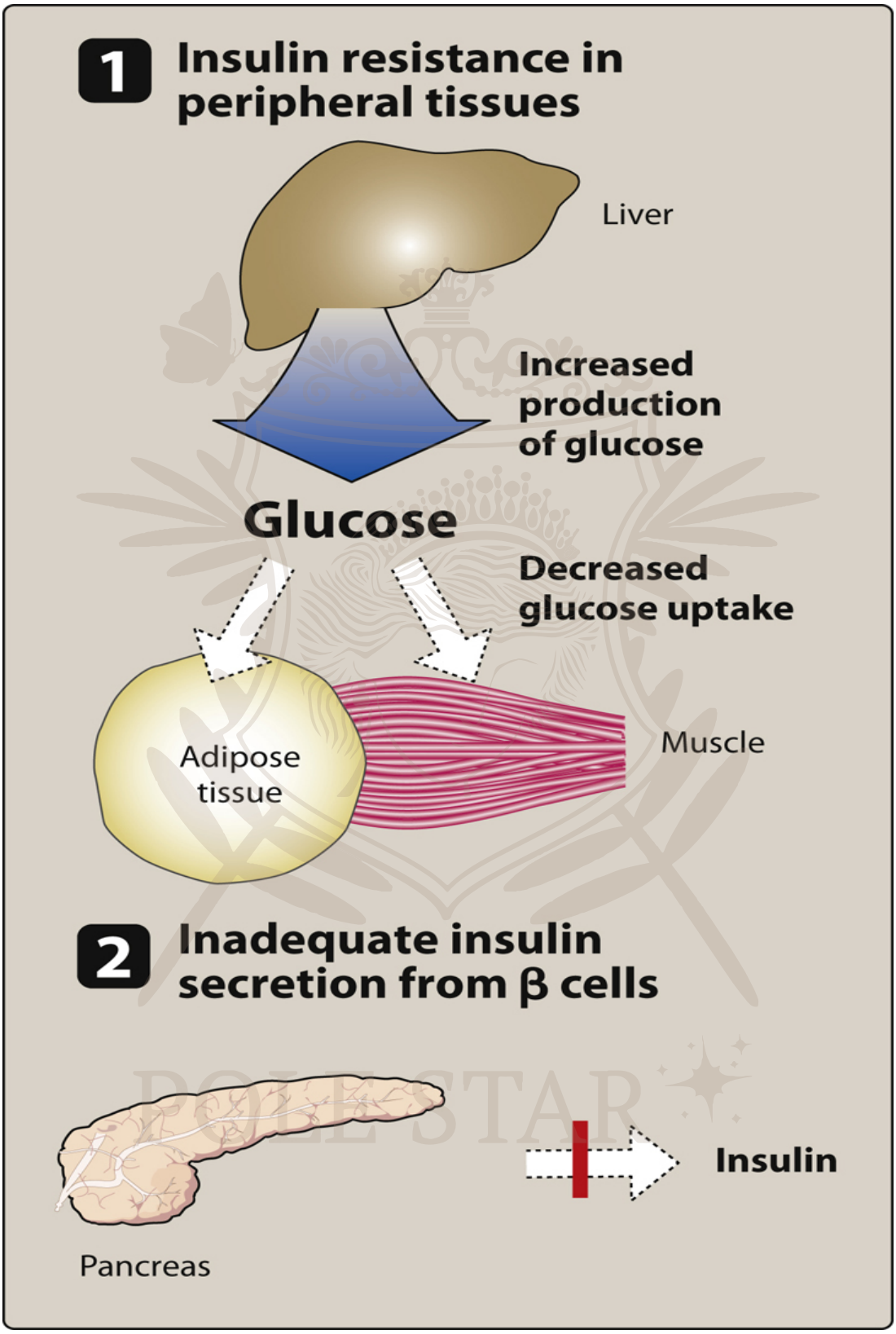

Figure 24.4 Major factors contributing to hyperglycemia in type 2 diabetes.

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2.Treatment: The goal in treating type 2 diabetes is to maintain blood glucose within normal range and to prevent the development of long-term complications. Weight reduction, exercise, and dietary modification decrease insulin resistance and correct hyperglycemia in patients with type 2 diabetes and should be part of a comprehensive diabetes management plan. Initial treatment for type 2 diabetes usually consists of oral glucose-lowering agents. Injectable agents (for example, glucagon-like peptide-1 agonists and insulin) may also be used in the management of type 2 diabetes. As the disease progresses, β-cell function declines, and insulin therapy is often needed to achieve satisfactory glucose levels (Figure 24.5).

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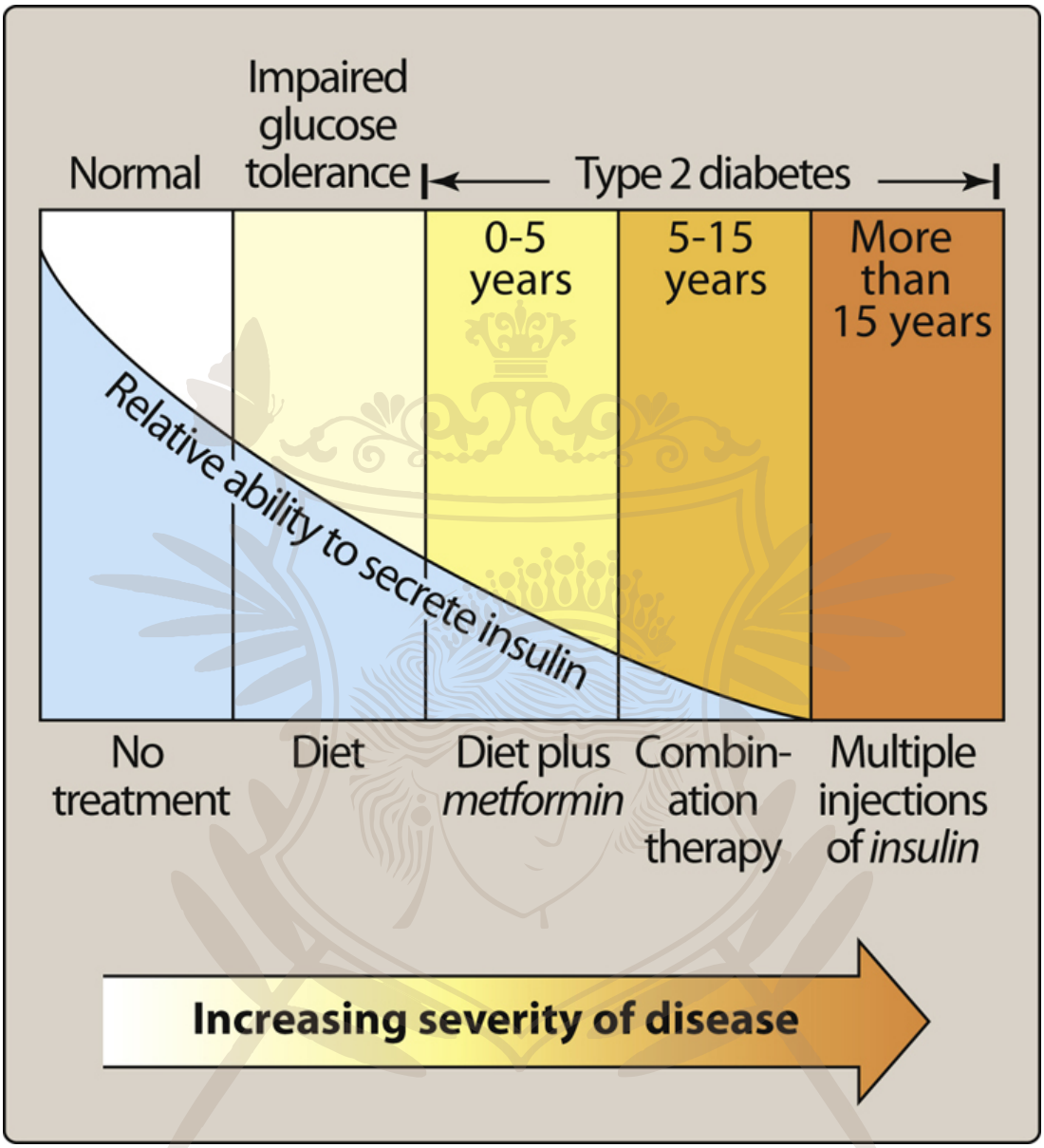

Figure 24.5 Duration of type 2 diabetes mellitus, sufficiency of endogenous insulin, and recommended sequence of therapy.Modified from M. C.Riddle . *Postgrad. Med*. 92: 89 (1992).

III. INSULIN

Insulin [IN-su-lin] is a polypeptide hormone consisting of two peptide chains that are connected by disulfide bonds. It is synthesized as a precursor (proinsulin) that undergoes proteolytic cleavage to form insulin

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and C-peptide, both of which are secreted by the β cells of the pancreas. [Note: Because insulin undergoes significant hepatic and renal extraction, plasma insulin levels may not accurately reflect insulin production. Thus, measurement of C-peptide provides a better index of insulin levels.]

A. Mechanism of action

Insulin secretion is regulated by blood glucose levels, certain amino acids, other hormones, and autonomic mediators. Secretion is most often triggered by increased blood glucose, which is taken up by the glucose transporter into the β cells of the pancreas. There, it is phosphorylated by glucokinase, which acts as a glucose sensor. The products of glucose metabolism enter the mitochondrial respiratory chain and generate adenosine triphosphate (ATP). The rise in ATP levels causes a blockade of K^+ channels, leading to membrane depolarization and an influx of Ca^{2+}. The increase in intracellular Ca^{2+} causes pulsatile insulin exocytosis. Exogenous insulin is administered to replace absent insulin secretion in type 1 diabetes or to supplement insufficient insulin secretion in type 2 diabetes.

B. Pharmacokinetics

Human insulin is produced by recombinant DNA technology using strains of Escherichia coli or yeast that are genetically altered to contain the gene for human insulin. Modification of the amino acid sequence of human insulin produces insulins with different pharmacokinetic properties. Insulin preparations vary primarily in their onset and duration of activity. Dose, injection site, blood supply, temperature, and physical activity can also affect the onset and duration of various insulin preparations. Because insulin is a polypeptide, it is degraded in the gastrointestinal tract if taken orally. Therefore, it is generally administered by subcutaneous injection, although an inhaled insulin formulation is also available. [Note: In a hyperglycemic emergency, *regular insulin* is administered intravenously (IV).] Continuous subcutaneous insulin infusion (also called the insulin pump) is another method of insulin delivery. This method of administration may be more convenient for some patients, especially for patients with type 1 diabetes, eliminating multiple daily injections of insulin. The pump is programmed to deliver a basal rate

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of insulin throughout the day. In addition, it also allows the patient to deliver a bolus of insulin to cover mealtime carbohydrate intake and compensate for high blood glucose.

C. Adverse effects

Hypoglycemia is the most serious and common adverse effect of insulin (Figure 24.6). Other adverse effects include weight gain, local injection site reactions, and lipodystrophy. Lipodystrophy can be minimized by rotation of injection sites. Diabetics with renal insufficiency may require a decrease in insulin dose. Due to the potential for bronchospasm with inhaled insulin, patients with asthma, chronic obstructive pulmonary disease, and smokers should not use this formulation.

POLE STAR

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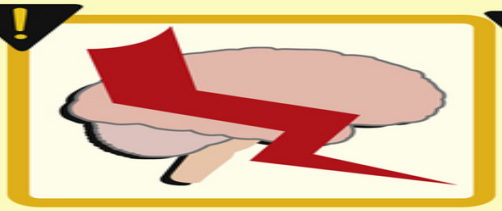
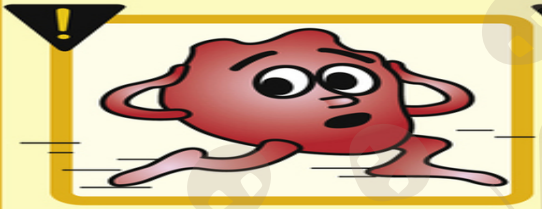
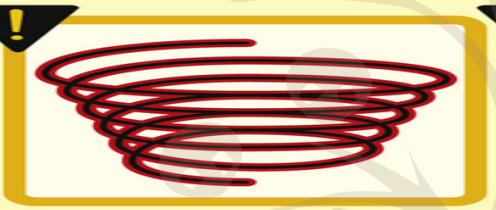
Symptoms caused by hypoglycemia

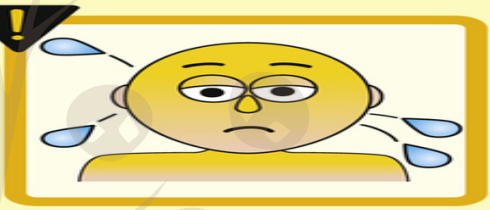

Headache

Anxiety


Tachycardia

Confusion


Vertigo


Diaphoresis

Shakiness

Increased appetite

Blurred vision

Weakness/ fatigue

Lipodystrophy

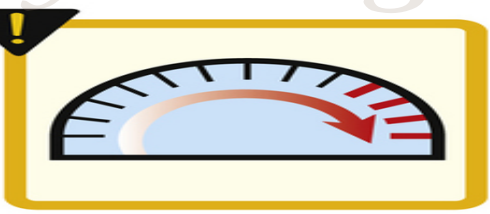

Weight gain

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Figure 24.6 Adverse effects observed with *insulin*.[Note: Lipodystrophy is a local atrophy or hypertrophy of subcutaneous fatty tissue at the site of injections.]

IV. INSULIN PREPARATIONS

Insulin preparations are classified as rapid-, short-, intermediate-, or long-acting. Figure 24.7 summarizes onset of action, timing of peak level, and duration of action for the various types of insulin. It is important that clinicians exercise caution when adjusting the insulin treatment plan, paying strict attention to the dose and type of insulin.

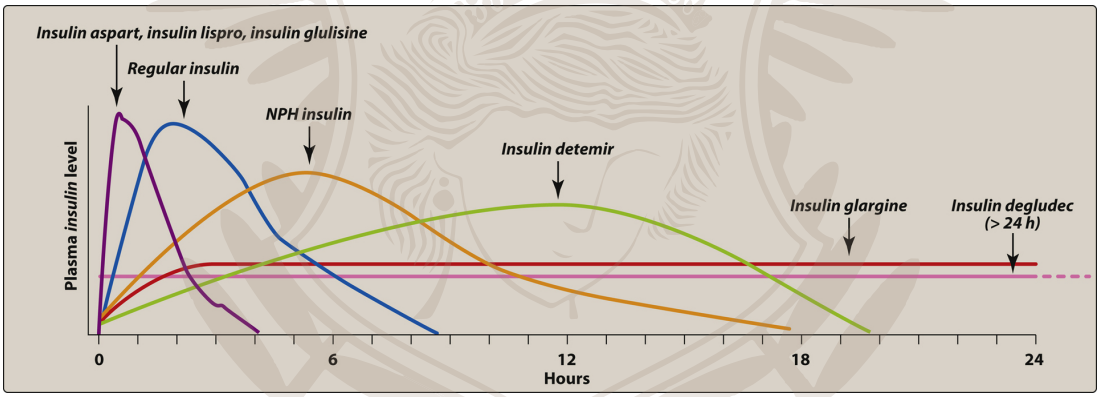

Figure 24.7 Onset and duration of action of human insulin and insulin analogs.NPH = neutral protamine Hagedorn.Modified from I. R.Hirsch . Insulin analogues. *N. Engl. J. Med*. 352: 174 (2005).

A. Rapid-Acting and short-acting insulin preparations

Five preparations fall into this category: *regular insulin*, *insulin lispro* [LIS-proe], *insulin aspart* [AS-part], *insulin glulisine* [gloo-LYSE-een], and *inhaled insulin. Regular insulin* is a short-acting, soluble, crystalline zinc insulin. Modification of the amino acid sequence of *regular insulin* produces analogs that are rapid acting. This modification results in more rapid absorption, a quicker onset, and a shorter duration of action after subcutaneous injection. *Insulin lispro*, *aspart*, and *glulisine* are classified as rapid-acting insulins. Peak levels

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of *insulin lispro* are seen 30 to 90 minutes after subcutaneous injection, as compared with 50 to 120 minutes for *regular insulin.* [Note: The onset of action of *insulin lispro* is 15 to 30 minutes, as compared with 30 minutes for *regular insulin*.] *Insulin aspart* and *insulin glulisine* have pharmacokinetic and pharmacodynamic properties similar to those of *insulin lispro.* These agents are available as an injectable solution or a prefilled insulin pen for injection. *Inhaled insulin* is also considered rapid acting. This dry powder formulation is inhaled and rapidly absorbed through pulmonary tissue, with peak insulin levels achieved within 10 to 20 minutes after inhalation.

Rapid- or short-acting insulins are administered to mimic the prandial (mealtime) release of insulin and to control postprandial glucose. They may also be used in cases where quick correction of elevated glucose is needed. Rapid- and short-acting insulins are usually used in conjunction with a longer-acting basal insulin that provides control of fasting glucose. *Regular insulin* should be injected subcutaneously 30 minutes before a meal, whereas rapid-acting insulins are administered 15 minutes preceding a meal or within 15 to 20 minutes after starting a meal. Rapid-acting insulin solutions are commonly used in insulin pumps, and they are suitable for IV administration, although *regular insulin* is most commonly used when the IV route is needed.

B. Intermediate-acting insulin

Neutral protamine Hagedorn (NPH) insulin is an intermediate-acting insulin formed by the addition of zinc and protamine to *regular insulin.* [Note: Another name for this preparation is *insulin isophane.*] The combination with protamine forms a complex that is less soluble, resulting in delayed absorption and a longer duration of action. *NPH insulin* is used as a basal insulin for fasting glucose control in type 1 or 2 diabetes and is usually given along with rapid- or short-acting insulin for mealtime control. *NPH insulin* should be administered subcutaneously (*never IV*), and it should not be used when rapid glucose lowering is needed (for example, diabetic ketoacidosis). [Note: A concentrated formulation of *regular insulin* (U-500) has pharmacokinetic properties more like that of intermediate-acting insulin. U-500 contains 500 units of insulin per mL and is 5 times more concentrated than most standard insulin preparations, which contain

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100 units/mL, U-100.] Figure 24.8 shows common regimens that use combinations of insulins.

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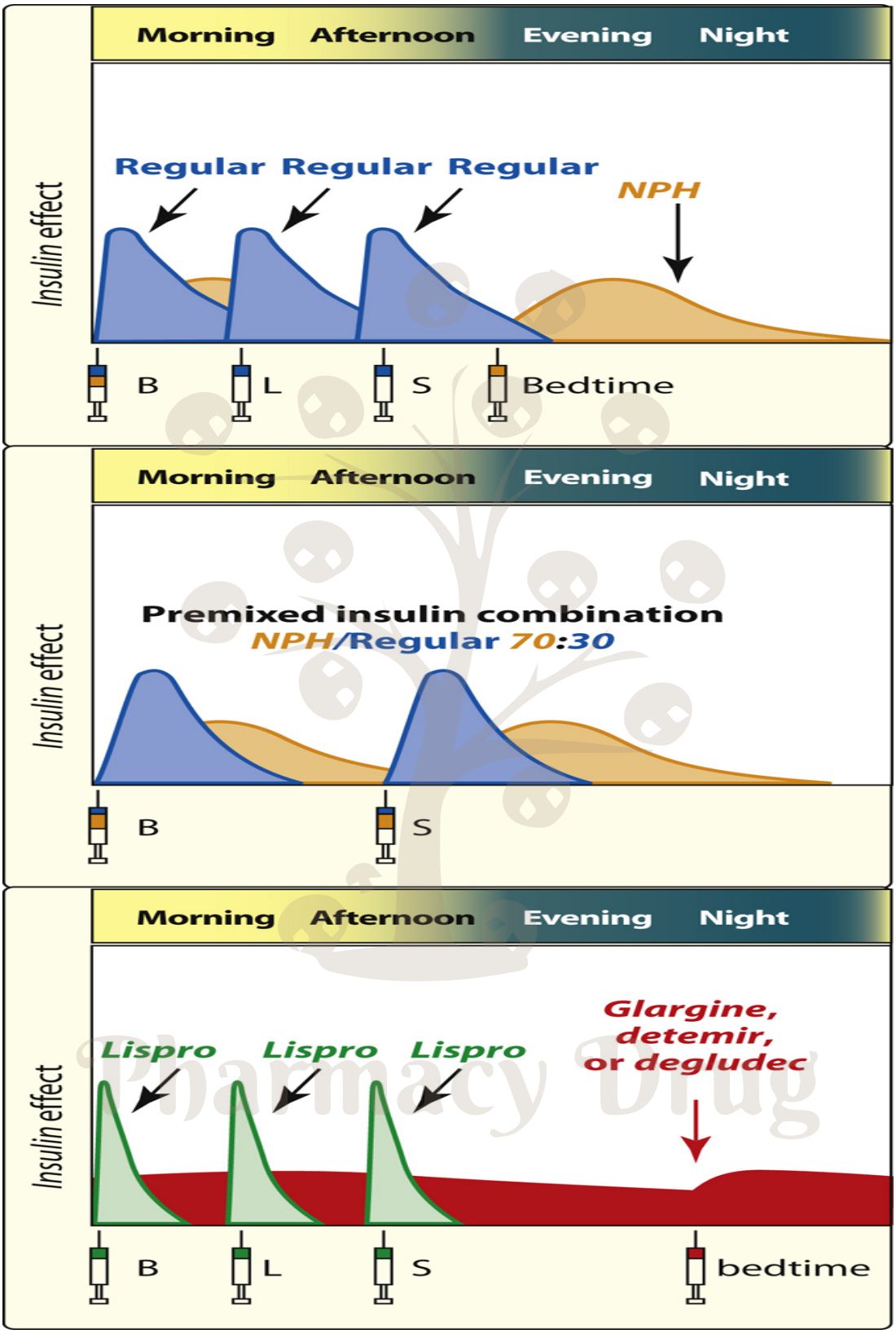

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Figure 24.8 Examples of three regimens that provide both prandial and basal *insulin* replacement.B = breakfast; L = lunch; S = supper; NPH = neutral protamine Hagedorn.

C. Long-Acting insulin preparations

The isoelectric point of *insulin glargine* [GLAR-geen] is lower than that of human insulin, leading to formation of a precipitate at the injection site that releases insulin over an extended period. It has a slower onset than *NPH insulin* and a flat, prolonged hypoglycemic effect with no peak (Figure 24.7). *Insulin detemir* [deh-TEE-meer] has a fatty acid side chain that enhances binding to albumin. Slow dissociation from albumin results in long-acting properties similar to those of *insulin glargine. Insulin degludec* [de-GLOO-dek] forms multihexamers when injected, resulting in a subcutaneous depot that slowly releases over an extended period. It has the longest half-life of the long-acting insulins. As with *NPH insulin*, *insulin glargine*, *insulin detemir*, and *insulin degludec* are used for basal control and should only be administered subcutaneously. Long-acting insulins should not be mixed in the same syringe with other insulins, as doing so may alter the pharmacodynamic profile.

D. Insulin combinations

Various premixed combinations of human insulins, such as 70% *NPH insulin* plus 30% *regular insulin* (Figure 24.8) or 50% of each of these, are also available. Use of premixed combinations decreases the number of daily injections but makes it more difficult to adjust individual components of the insulin regimen.

E. Standard treatment versus intensive treatment

Standard insulin therapy involves twice-daily injections. In contrast, intensive treatment utilizes three or more injections daily with frequent monitoring of blood glucose levels. The ADA recommends a target mean blood glucose level of 154 mg/dL or less (A1C ≤ 7%) for most patients, and intensive treatment is more likely to achieve this goal. The frequency of hypoglycemic episodes, coma, and seizures is higher with intensive insulin regimens (Figure 24.9A). However, patients on intensive therapy show a significant reduction in

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microvascular complications of diabetes such as retinopathy, nephropathy, and neuropathy compared with patients receiving standard therapy (Figure 24.9B). Intensive therapy should not be recommended for patients with long-standing diabetes, significant microvascular complications, advanced age, and those with hypoglycemic unawareness.

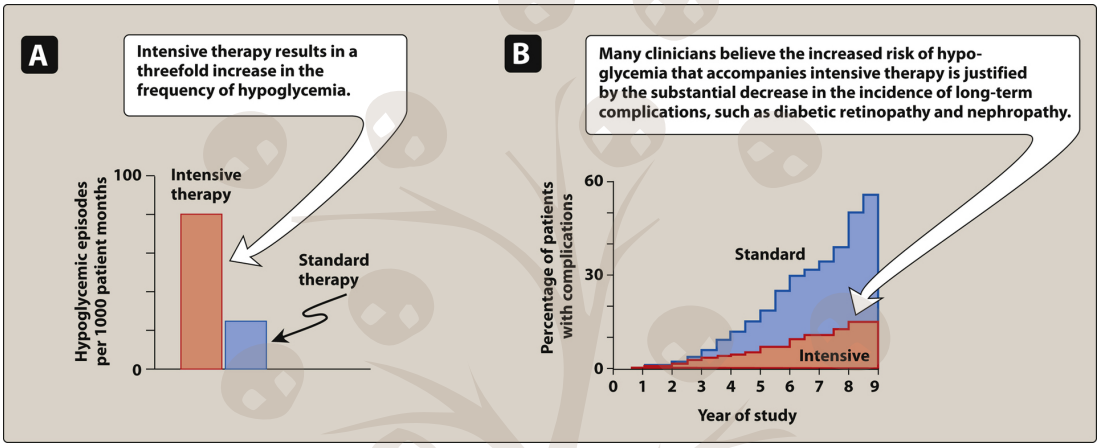

Figure 24.9 **A.** Effect of tight glucose control on hypoglycemic episodes in a population of patients with type 1 diabetes receiving intensive or standard therapy. **B.** Effect of standard and intensive care on the long-term complications of diabetes.Data from O. B.Crofford . Diabetes control and complications. *Annu. Rev. Med*. 46: 267 (1995).

V. AMYLIN ANALOG

Amylin is a hormone that is cosecreted with insulin from β cells following food intake. It delays gastric emptying, decreases postprandial glucagon secretion, and improves satiety. *Pramlintide* [PRAM-lin-tide] is a synthetic amylin analog that is indicated as an adjunct to mealtime insulin in patients with type 1 and type 2 diabetes. *Pramlintide* is administered by subcutaneous injection immediately before meals. When *pramlintide* is initiated, the dose of mealtime insulin should be decreased by 50% to avoid a risk of severe hypoglycemia. Other adverse effects include nausea, anorexia, and vomiting. *Pramlintide* may not be mixed in the

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same syringe with insulin, and it should be avoided in patients with diabetic gastroparesis (delayed stomach emptying), cresol hypersensitivity, or hypoglycemic unawareness.

VI. GLUCAGON-LIKE PEPTIDE RECEPTOR AGONISTS

Oral intake of glucose results in a higher secretion of insulin than occurs when an equal amount of glucose is administered IV. This effect is referred to as the "incretin effect" and is markedly reduced in type 2 diabetes. The incretin effect occurs because the gut releases incretin hormones, notably glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), in response to a meal. Incretin hormones are responsible for 60% to 70% of postprandial insulin secretion. *Dulaglutide* [doo-la-GLOO-tide], *exenatide* [EX-e-nah-tide], *liraglutide* [LIR-a-GLOO-tide], *lixisenatide* [lix-i-SEN-a-tide], and *semaglutide* [sem-a-GLOO-tide] are injectable GLP-1 receptor agonists used for the treatment of type 2 diabetes. [Note: *Semaglutide* is also available in an oral formulation.] *Dulaglutide*, *liraglutide,* and *semaglutide* are also approved to reduce the risk of cardiovascular mortality in patients with type 2 diabetes and cardiovascular disease. Two premixed preparations of long-acting insulins and GLP-1 receptor agonists are available: *insulin glargine* plus *lixisenatide* and *insulin degludec* plus *liraglutide.* Use of these combinations may decrease daily insulin requirements and the number of daily injections.

A. Mechanism of action

The GLP-1 receptor agonists improve glucose-dependent insulin secretion, slow gastric emptying time, reduce food intake by enhancing satiety (a feeling of fullness), decrease postprandial glucagon secretion, and promote β-cell proliferation. Consequently, postprandial hyperglycemia is reduced, A1C levels decrease, and weight loss may occur. [Note: Higher dosages of injectable *semaglutide* and *liraglutide* are approved for the treatment of obesity.]

B. Pharmacokinetics

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GLP-1 receptor agonists are administered subcutaneously, since they are polypeptides. *Dulaglutide*, *liraglutide*, and *semaglutide* are considered long-acting GLP-1 receptor agonists. *Dulaglutide* and *semaglutide* are dosed once weekly, while *liraglutide* is available as a once-daily injection. The oral formulation of *semaglutide* is dosed once daily. *Lixisenatide* is a short-acting GLP-1 receptor agonist that is dosed once daily. *Exenatide* is available as both a short-acting (dosed twice daily) and extended-release preparation (dosed once weekly). *Exenatide* should be avoided in patients with severe renal impairment.

C. Adverse effects

The main adverse effects of the GLP-1 receptor agonists consist of nausea, vomiting, diarrhea, and constipation. These agents have been associated with pancreatitis and should be avoided in patients with chronic pancreatitis. Longer-acting agents have been associated with thyroid C-cell tumors in rodents. It is unknown if GLP-1 receptor agonists cause these tumors or thyroid carcinoma in humans, although they are contraindicated in patients with a history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2.

VII. ORAL AGENTS

Oral agents are useful in the treatment of patients with type 2 diabetes. Patients who have had diabetes less than 5 years are most likely to respond well to oral glucose-lowering agents. Patients with long-standing disease may require a combination of oral agents with or without insulin or GLP-1 receptor agonists to control hyperglycemia. Figure 24.10 summarizes the duration of action of some of the oral glucose-lowering drugs, and Figure 24.11 illustrates some of the common adverse effects.

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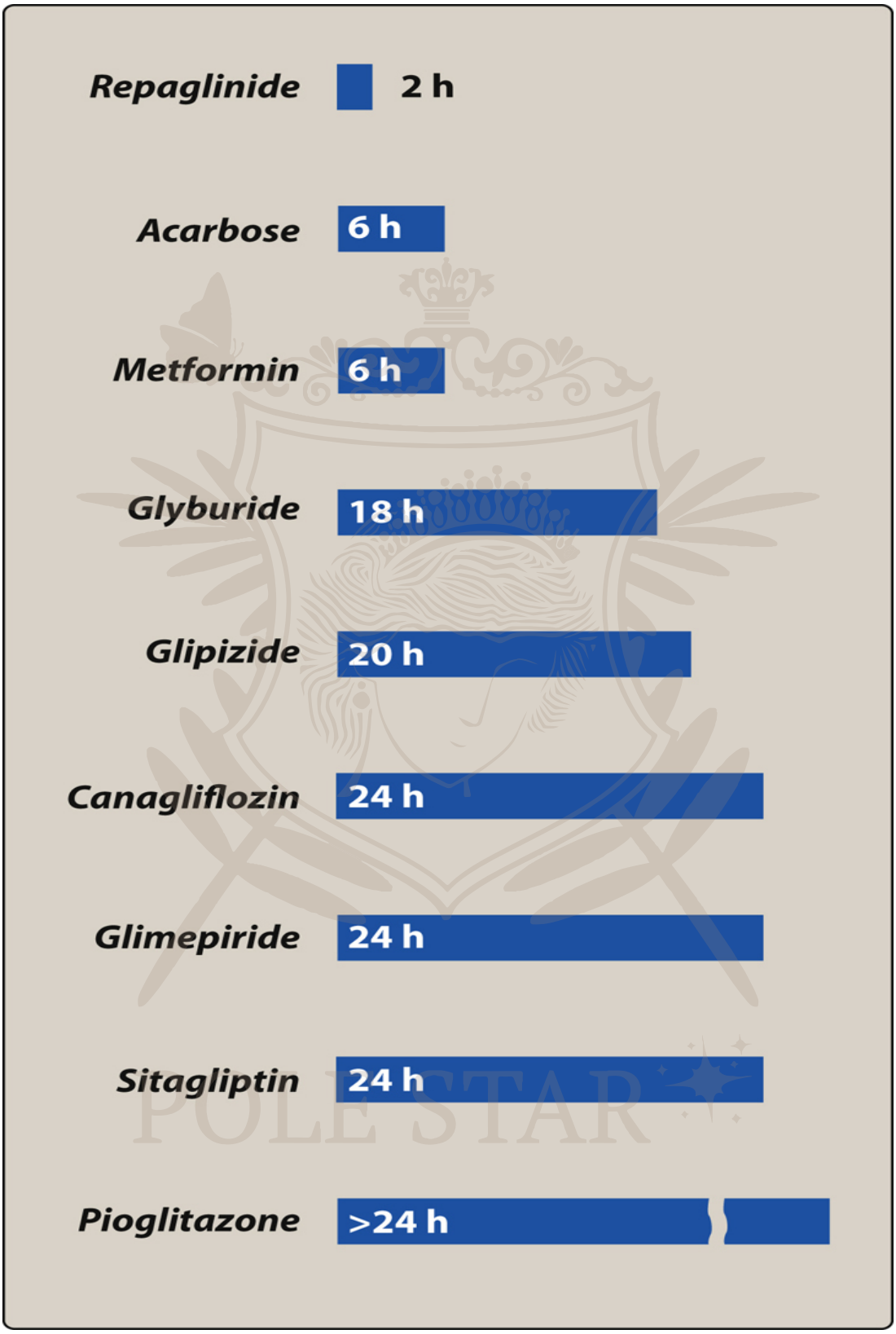

Figure 24.10 Duration of action of some oral hypoglycemic agents.

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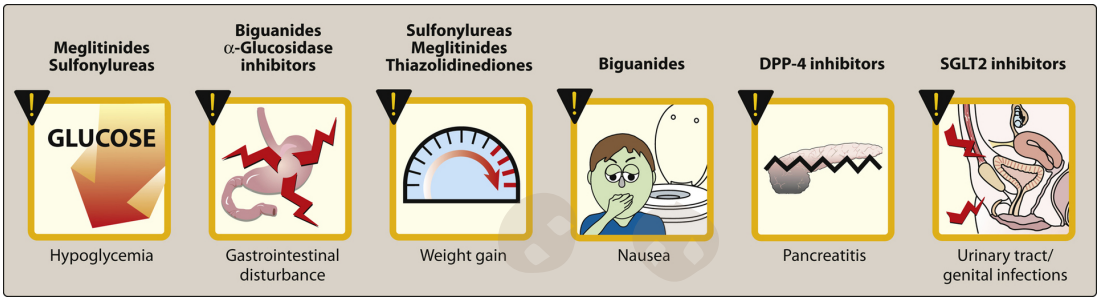

Figure 24.11 Some adverse effects with oral hypoglycemic agents.DPP-4 = dipeptidyl peptidase-4; SGLT2 = sodium–glucose cotransporter 2.

A. Biguanides

Metformin [met-FOR-min], the only biguanide, is the preferred initial therapy for type 2 diabetes, and the drug should be initiated upon diagnosis. It is also beneficial in the prevention of type 2 diabetes in patients with prediabetes. [Note: *Metformin* is also useful in the treatment of polycystic ovary syndrome, as it reduces insulin resistance associated with this disorder.]

1.Mechanism of action: The main mechanism of action of *metformin* is reduction of hepatic gluconeogenesis. [Note: Excess glucose produced by the liver is a major source of high blood glucose in type 2 diabetes, accounting for high fasting blood glucose.] *Metformin* also slows intestinal absorption of sugars and improves peripheral glucose uptake and utilization (improves insulin sensitivity). The drug does not promote insulin secretion. Therefore, the risk of hypoglycemia with *metformin* is far less than that with other agents that enhance insulin secretion (for example, sulfonylureas). *Metformin* may be used alone or in combination with other oral agents or injectables. Hypoglycemia may occur when *metformin* is taken in combination with insulin or insulin secretagogues, so adjustment in dosage may be required.

2.Pharmacokinetics: *Metformin* is well absorbed after oral administration, is not bound to serum proteins, and is not

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metabolized. Excretion is primarily via the kidneys as unchanged drug.

3.Adverse effects: These are largely gastrointestinal, including diarrhea, nausea, and vomiting. These effects can be alleviated by titrating the dose of *metformin* slowly and administering the drug with meals. Weight loss may occur because *metformin* causes loss of appetite. *Metformin* is contraindicated in severe renal dysfunction (estimated glomerular filtration rate less than 30 mL/min/1.73 m^2) due to the risk of lactic acidosis. It should be discontinued in cases of acute myocardial infarction, exacerbation of heart failure, sepsis, or other disorders that can cause acute renal failure. *Metformin* should be used with caution in patients older than 80 years and in those with a history of alcohol abuse. It should be temporarily discontinued in patients undergoing procedures requiring IV radiographic contrast. Rarely, potentially fatal lactic acidosis has occurred. Long-term use may be associated with vitamin B_{12} deficiency, and periodic measurement of vitamin B_{12} levels is recommended, especially in patients with anemia or peripheral neuropathy.

B. Sulfonylureas

These agents are classified as insulin secretagogues, because they promote insulin release from the β cells of the pancreas. The sulfonylureas most used in clinical practice are the second-generation drugs *glyburide* [GLYE-byoor-ide], *glipizide* [GLIP-ih-zide], and *glimepiride* [GLYE-me-pih-ride].

1.Mechanism of action: The primary mechanism of action is stimulation of insulin release from the β cells of the pancreas. Sulfonylureas block ATP-sensitive K^+ channels on the β cells, resulting in depolarization, Ca^{2+} influx, and exocytosis of insulin. In addition, sulfonylureas may reduce hepatic glucose production and increase peripheral insulin sensitivity.

2.Pharmacokinetics: Given orally, these drugs bind to serum proteins, are metabolized by the liver, and are excreted in the urine and feces. The duration of action ranges from 12 to 24 hours.

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3.Adverse effects: Adverse effects of the sulfonylureas include hypoglycemia, hyperinsulinemia, and weight gain. They should be used with caution in hepatic or renal insufficiency, since accumulation of sulfonylureas may cause hypoglycemia. Renal impairment is a particular problem for *glyburide*, as it may increase the duration of action and increase the risk of hypoglycemia significantly. *Glipizide* or *glimepiride* are safer options in renal dysfunction and in elderly patients. Figure 24.12 summarizes some drug interactions with sulfonylureas.

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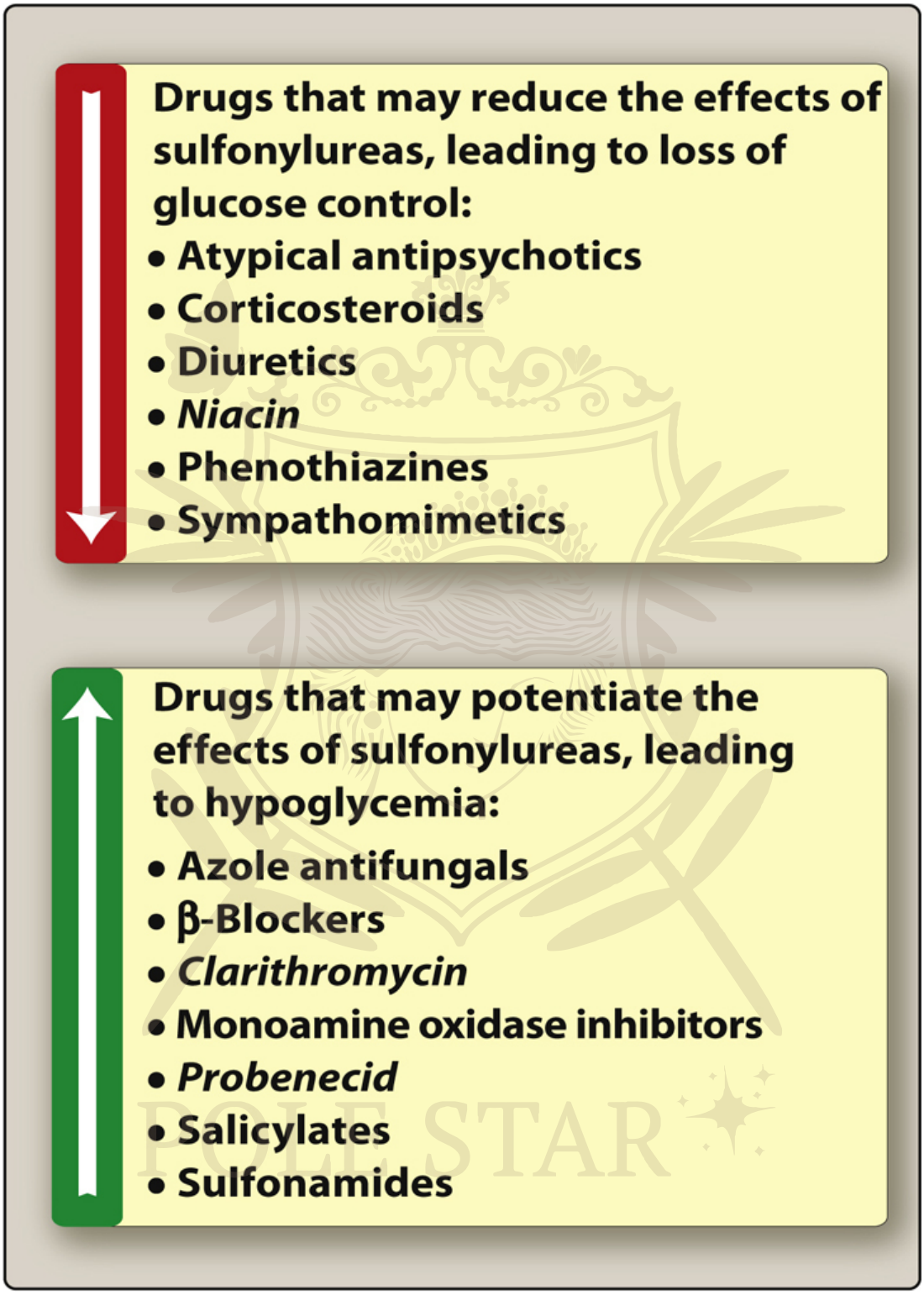

Figure 24.12 Drugs interacting with sulfonylureas.

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C. Meglitinides

This class of agents includes *repaglinide* [re-PAG-lin-ide] and *nateglinide* [nuh-TAY-gli-nide]. The meglitinides are also considered insulin secretagogues.

1.Mechanism of action: Like the sulfonylureas, the meglitinides stimulate insulin secretion. In contrast to the sulfonylureas, the meglitinides have a rapid onset and a shorter duration of action. They are particularly effective in the early release of insulin that occurs after a meal and are categorized as postprandial glucose regulators. Meglitinides should not be used in combination with sulfonylureas due to an overlapping mechanism of action and increased risk of serious hypoglycemia.

2.Pharmacokinetics: Meglitinides should be taken prior to a meal and are well absorbed after oral administration. *Nateglinide* is primarily metabolized via CYP2C9 and CYP3A4, and metabolites are excreted in the urine. *Repaglinide* is metabolized to inactive products by CYP2C8 and CYP3A4 in the liver, and the drug and its metabolites are excreted in the feces.

3.Adverse effects: Although meglitinides cause hypoglycemia and weight gain, the incidence is lower than that with sulfonylureas. By inhibiting hepatic metabolism, the lipid-lowering drug *gemfibrozil* may significantly increase the effects of *repaglinide*, and concurrent use is contraindicated. These agents should be used with caution in patients with hepatic impairment.

D. Thiazolidinediones

The thiazolidinediones (TZDs) are insulin sensitizers. The two agents in this class are *pioglitazone* [pye-oh-GLI-ta-zone] and *rosiglitazone* [roe-si-GLIH-ta-zone]. Although insulin is required for their action, the TZDs do not promote its release from the β cells, so hyperinsulinemia is not a risk.

1.Mechanism of action: The TZDs lower insulin resistance by acting as agonists for the peroxisome proliferator–activated receptor-γ (PPARγ), a nuclear hormone receptor. Activation of PPARγ regulates the transcription of several insulin responsive

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genes, resulting in increased insulin sensitivity in adipose tissue, liver, and skeletal muscle. The TZDs can be used as monotherapy or in combination with other glucose-lowering agents or insulin. The dose of insulin may have to be lowered when used in combination with these agents. *Rosiglitazone* is less utilized due to concerns regarding cardiovascular adverse effects.

2.Pharmacokinetics: *Pioglitazone* and *rosiglitazone* are well absorbed after oral administration and are extensively bound to serum albumin. Both drugs undergo extensive metabolism, primarily by CYP2C8. Some metabolites of *pioglitazone* have activity. Renal elimination of *pioglitazone* is negligible, with the majority of active drug and metabolites excreted in the bile and eliminated in the feces. Metabolites of *rosiglitazone* are primarily excreted in the urine. No dosage adjustment is required in renal impairment.

3.Adverse effects: Weight gain can occur because TZDs may increase subcutaneous fat and cause fluid retention. [Note: Fluid retention can worsen heart failure. These drugs should be avoided in patients with symptomatic heart failure.] TZDs have been associated with osteopenia and increased fracture risk in women. *Pioglitazone* may also increase the risk of bladder cancer. Additionally, *rosiglitazone* carries a boxed warning about the potential increased risk of myocardial infarction and angina with the use of this agent. Liver toxicity has occasionally been reported with these drugs, and baseline and periodic monitoring of liver function is recommended.

E. Dipeptidyl peptidase-4 inhibitors

Alogliptin [al-oh-GLIP-tin], *linagliptin* [lin-a-GLIP-tin], *saxagliptin* [sax-a-GLIP-tin], and *sitagliptin* [si-ta-GLIP-tin] are oral dipeptidyl peptidase-4 (DPP-4) inhibitors used for the treatment of type 2 diabetes.

1.Mechanism of action: These drugs inhibit the enzyme DPP-4, which is responsible for the inactivation of incretin hormones such as GLP-1 (Figure 24.13). Prolonging the activity of incretin hormones increases release of insulin in response to meals and reduces inappropriate secretion of glucagon. DPP-4 inhibitors may

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be used as monotherapy or in combination with sulfonylureas, *metformin*, TZDs, or insulin. Treatment guidelines do not recommend the combination of DPP-4 inhibitors with GLP-1 receptor agonists for management of diabetes due to overlapping mechanisms of action and increased potential for toxicity. Unlike GLP-1 receptor agonists, these drugs do not cause satiety or fullness and are weight neutral.

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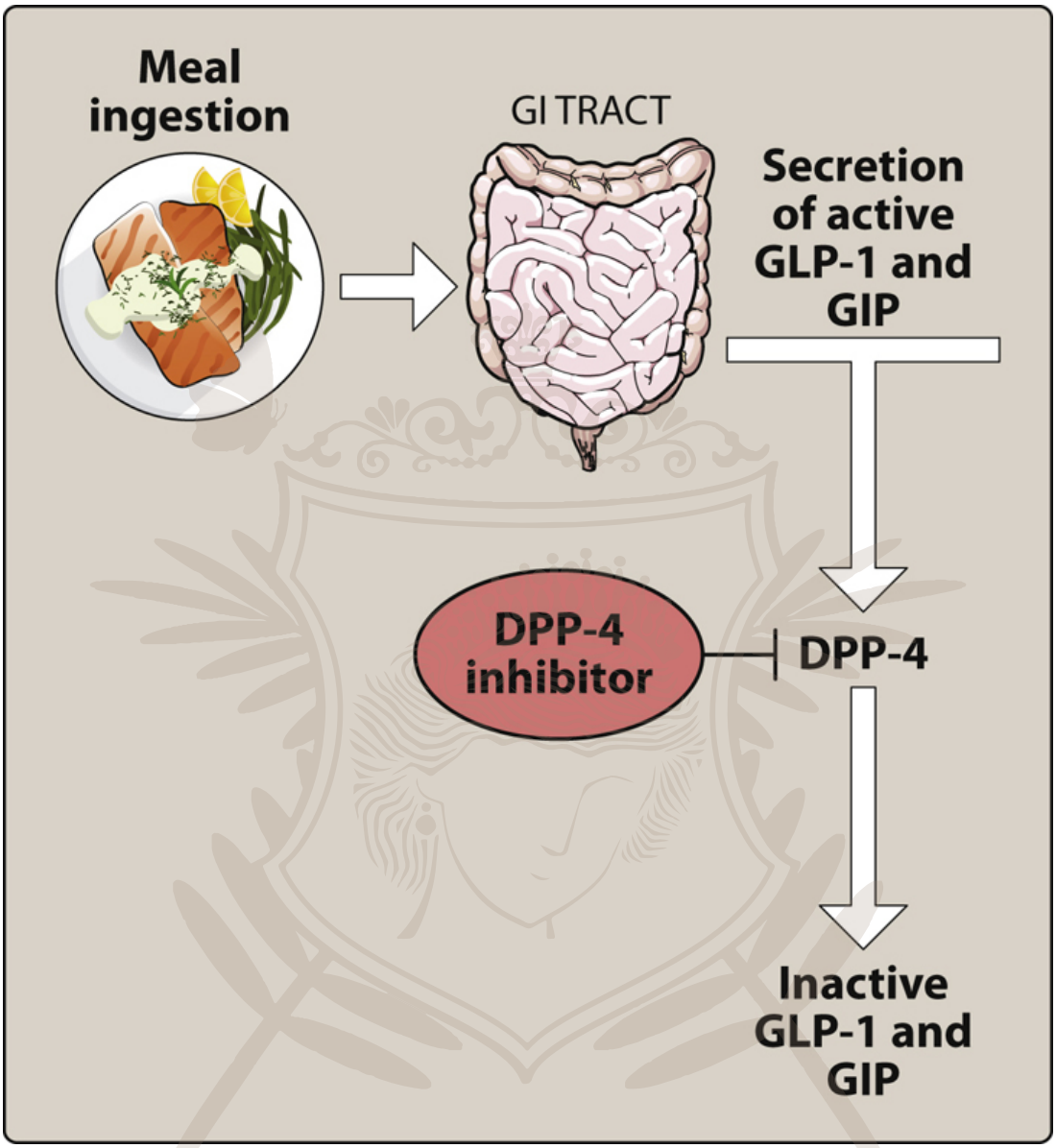

Figure 24.13 Mechanism of action of DPP-4 inhibitors.DPP-4 = dipeptidyl peptidase-4. GIP = glucose-dependent insulinotropic peptide; GLP-1 = glucagon-like peptide-1.

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2.Pharmacokinetics: The DPP-4 inhibitors are well absorbed after oral administration. Food does not affect the extent of absorption. *Alogliptin* and *sitagliptin* are mostly excreted unchanged in the urine. *Saxagliptin* is metabolized via CYP450 3A4/5 to an active metabolite. The primary route of elimination for *saxagliptin* and the metabolite is renal. *Linagliptin* is primarily

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eliminated via the enterohepatic system. All DPP-4 inhibitors except *linagliptin* require dosage adjustments in renal dysfunction.

3.Adverse effects: In general, DPP-4 inhibitors are well tolerated, with nasopharyngitis and headache as the most common adverse effects. Although infrequent, serious hypersensitivity reactions and pancreatitis have occurred with the use of DPP-4 inhibitors. Agents in this class may also increase the risk of joint pain, which is severe and disabling in some cases. *Saxagliptin* has also been shown to increase the risk of heart failure hospitalizations and should be used with caution in patients with or at risk for heart failure.

F. Sodium–glucose cotransporter 2 inhibitors

Canagliflozin [kan-a-gli-FLOE-zin], *dapagliflozin* [dap-a-gli-FLOE-zin], *empagliflozin* [em-pa-gli-FLOE-zin], and *ertugliflozin* [er-too-gli-FLOE-zin] are oral sodium–glucose cotransporter 2 inhibitors for the treatment of type 2 diabetes. *Canagliflozin* and *empagliflozin* are also indicated to reduce the risk of cardiovascular death in patients with type 2 diabetes and cardiovascular disease. In addition, *canagliflozin* and *dapagliflozin* have been shown to reduce the risk of heart failure hospitalizations and end-stage kidney disease in patients with type 2 diabetes. [Note: *Dapagliflozin* and *empagliflozin* are also indicated for the treatment of heart failure with reduced ejection fraction (see Chapter 10).]

1.Mechanism of action: The sodium–glucose cotransporter 2 (SGLT2) is responsible for reabsorbing filtered glucose in the tubular lumen of the kidney. By inhibiting SGLT2, these agents decrease reabsorption of glucose, increase urinary glucose excretion, and lower blood glucose (Figure 24.14). Inhibition of SGLT2 also decreases reabsorption of sodium and causes osmotic diuresis. Therefore, SGLT2 inhibitors may reduce systolic blood pressure. However, they are not indicated for the treatment of hypertension.

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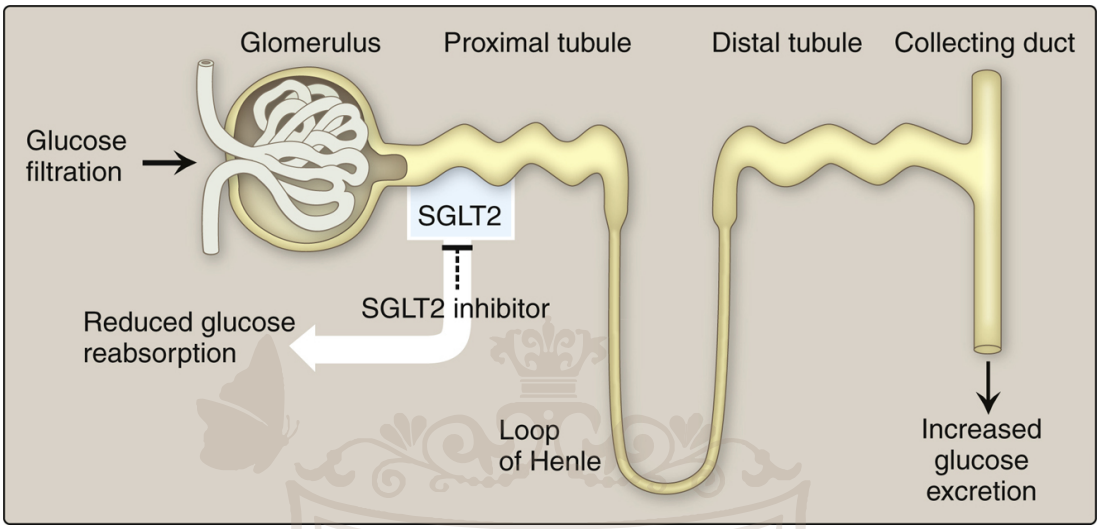

Figure 24.14 Mechanism of action of sodium–glucose cotransporter 2 (SGLT2) inhibitors.

2.Pharmacokinetics: These agents are given once daily in the morning. *Canagliflozin* should be taken before the first meal of the day. All drugs are mainly metabolized by glucuronidation to inactive metabolites. These agents should be avoided in patients with severe renal dysfunction.

3.Adverse effects: The most common adverse effects with SGLT2 inhibitors are female genital mycotic infections (for example, vulvovaginal candidiasis), urinary tract infections, and urinary frequency. Hypotension has also occurred, particularly in the elderly or patients on diuretics. Thus, volume status should be evaluated prior to starting these agents. Ketoacidosis has been reported with use of SGLT2 inhibitors, and these agents should be used with caution in patients with risk factors that predispose to ketoacidosis (for example, alcohol abuse and caloric restriction related to surgery or illness). SGLT2 inhibitors are also associated with an increased risk of bone fractures and Fournier gangrene.

G. α-Glucosidase inhibitors

Acarbose [AY-car-bose] and *miglitol* [MIG-li-tol] are oral agents used for the treatment of type 2 diabetes.

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1.Mechanism of action: Located in the intestinal brush border, α-glucosidase enzymes break down carbohydrates into glucose and other simple sugars that can be absorbed. *Acarbose* and *miglitol* reversibly inhibit α-glucosidase enzymes. When taken at the start of a meal, these drugs delay the digestion of carbohydrates, resulting in lower postprandial glucose levels. Since they do not stimulate insulin release or increase insulin sensitivity, these agents do not cause hypoglycemia when used as monotherapy. However, when used with insulin secretagogues or insulin, hypoglycemia may develop. [Note: It is important that hypoglycemia in this context be treated with glucose rather than sucrose, because sucrase is also inhibited by these drugs.]

2.Pharmacokinetics: *Acarbose* is poorly absorbed. It is metabolized primarily by intestinal bacteria, and some of the metabolites are absorbed and excreted into the urine. *Miglitol* is very well absorbed but has no systemic effects. It is excreted unchanged by the kidney.

3.Adverse effects: The most common adverse effects are flatulence, diarrhea, and abdominal cramping. Adverse effects limit the use of these agents in clinical practice. Patients with inflammatory bowel disease, colonic ulceration, or intestinal obstruction should not use these drugs.

H. Other agents

Both the dopamine agonist *bromocriptine* and the bile acid sequestrant *colesevelam* produce modest reductions in A1C. The mechanism of action of glucose lowering is unknown for both of these drugs. Although *bromocriptine* and *colesevelam* are indicated for the treatment of type 2 diabetes, their modest efficacy, adverse effects, and pill burden limit their use in clinical practice.

Figure 24.15 provides a summary of the oral antidiabetic agents and GLP-1 receptor agonists.

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DRUG CLASS	MECHANISM OF ACTION	RISK OF HYPOGLYCEMIA	COMMENTS
Biguanides *Metformin*	Decreases hepatic production of glucose	No	Preferred agent in type 2 diabetes. Monitor renal function and vitamin B12 levels. Avoid in severe renal impairment.
Sulfonylureas *Glimepiride* *Glipizide* *Glyburide*	Stimulates insulin secretion	Yes	Weight gain can occur. Hypoglycemia most common with this class of oral agents. Avoid *glyburide* in renal impairment.
Meglitinides *Nateglinide* *Repaglinide*	Stimulates insulin secretion	Yes (rarely)	Taken with meals. Short action with less hypoglycemia. Postprandial effect.
Thiazolidinediones *Pioglitazone* *Rosiglitazone*	Binds to peroxisome proliferator–activated receptor-γ in muscle, fat and liver to decrease insulin resistance	No	Effective in highly insulin-resistant patients. Once-daily dosing for *pioglitazone*. Check liver function before initiation. Avoid in liver disease or heart failure.
DPP-4 inhibitors *Alogliptin* *Linagliptin* *Sitagliptin* *Saxagliptin*	Increases glucose-dependent insulin release; decreases secretion of glucagon	No	Once-daily dosing. May be taken with or without food. Well tolerated. Risk of pancreatitis. All require renal dose adjustment, except *linagliptin*. Do not combine with GLP-1 receptor agonists
SGLT2 inhibitors *Canagliflozin* *Dapaglifozin* *Empagliflozin* *Ertugliflozin*	Increases urinary glucose excretion	No	Once-daily dosing in the morning. Risk of hypotension, genitourinary infections. Avoid in severe renal impairment. *Canagliflozin* and *empagliflozin* are approved to reduce cardiovascular mortality in patients with type 2 diabetes. *Dapagliflozin* and *empagliflozin* are also indicated for the treatment of HFrEF.
α-Glucosidase inhibitors *Acarbose* *Miglitol*	Decreases glucose absorption	No	Taken with meals. Adverse gastrointestinal effects. Not a preferred therapy. Reserve for patients unable to tolerate other agents.
GLP-1 receptor agonists *Dulaglutide* *Exenatide* *Liraglutide* *Lixisenatide* *Semaglutide*	Increases glucose-dependent insulin release; decreases secretion of glucagon; slows gastric emptying; increases satiety	No	Injectable formulation. *Liraglutide* and *lixisenatide* are dosed once daily. *Dulaglutide* and *semaglutide* are dosed once weekly. *Semaglutide* is also available in an oral formulation. *Exenatide* is dosed twice daily and extended-release *exenatide* is dosed once weekly. *Dulaglutide, liraglutide,* and *semaglutide* are approved to reduce cardiovascular events in patients with type 2 diabetes. Weight loss may occur. Risk of pancreatitis. Contraindicated in patients with a history of medullary thyroid carcinoma.

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Figure 24.15 Summary of oral agents and GLP-1 receptor agonists used to treat diabetes.⇔ = little or no change; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HFrEF = heart failure with reduced ejection fraction; SGLT2 = sodium–glucose cotransporter 2.

Figure 24.16 shows treatment guidelines for type 2 diabetes.

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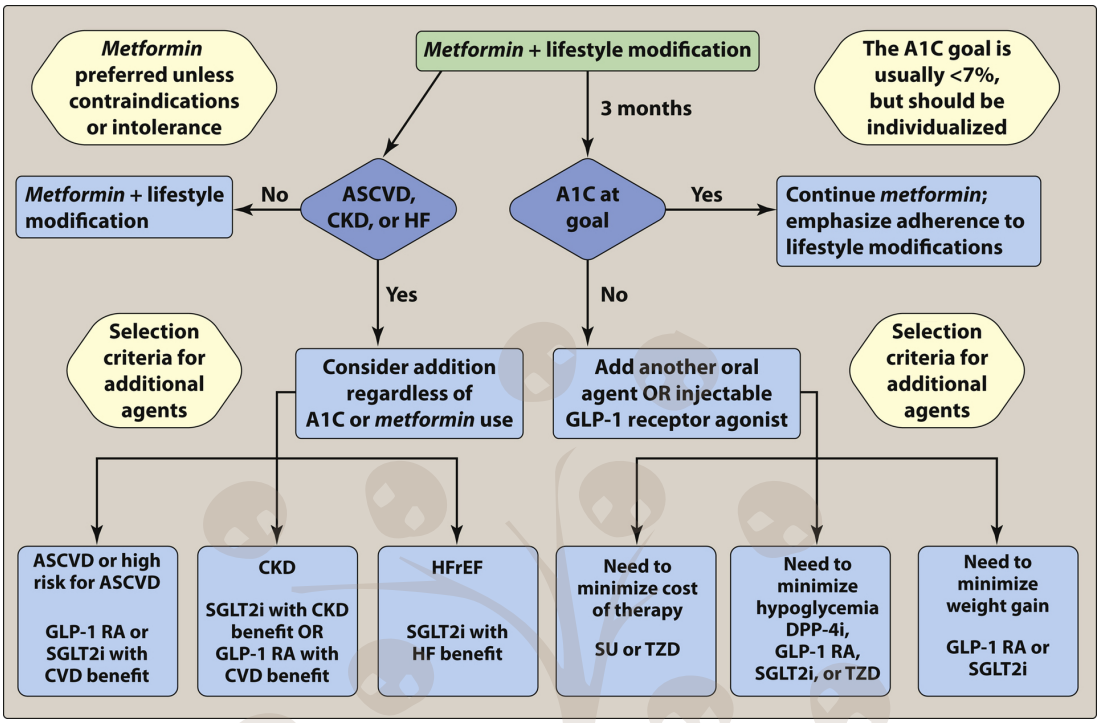

Figure 24.16 Recommendations for the management of type 2 diabetes.A1C = glycosylated hemoglobin; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CVD = cardiovascular disease; DPP-4i = dipeptidyl peptidase inhibitor; GLP-1 RA = glucagon-like peptide 1 receptor agonist; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; SGLT2i = sodium–glucose cotransporter 2 inhibitor; SU = sulfonylurea; TZD = thiazolidinedione.

Clinical Application 24.3: Drug Therapy for Type 2 Diabetes

The biguanide *metformin* is the preferred initial agent for management of type 2 diabetes. The efficacy, low cost, and safety of *metformin* are the reasons for its recommendation as the drug of choice. [Note: Patients with intolerance or contraindications to *metformin* should be treated with alternative agents with cardiovascular or renal benefits.] In addition to initiation of *metformin*, patients with type 2 diabetes and atherosclerotic cardiovascular disease, chronic kidney disease, or heart failure with reduced ejection fraction should be evaluated for the need for additional agents (usually GLP-1 receptor agonists or sodium–glucose cotransporter 2 inhibitors), which demonstrate reduction in mortality or progression of these coexisting disorders (Figure 24.16). Patients who do not obtain the target A1C with *metformin* are candidates for the addition of another agent for the management of type 2 diabetes. The additional agent should be selected based on patient-specific

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characteristics, such as the need to minimize cost of therapy, hypoglycemia, or weight gain.

Chapter Summary

- Type 1 diabetes is characterized by an absolute deficiency of insulin. Insulin is the treatment for type 1 diabetes.
- Rapid-acting (*insulin aspart*, *glulisine*, or *lispro*) or short-acting insulins (*regular insulin*) are used for mealtime glycemic control or situations where quick reduction or correction of blood glucose is needed.
- Intermediate (*NPH insulin*) or long-acting insulins (*insulin degludec*, *detemir*, or *glargine*) are used for basal control of glucose. The need for adjustment of basal insulin is assessed with fasting glucose levels.
- Hypoglycemia, weight gain, and lipodystrophy are adverse effects of insulin therapy.
- *Pramlintide* is a synthetic amylin analog that may be used for additional mealtime glycemic control in type 1 or type 2 diabetes.
- Type 2 diabetes is characterized by insulin resistance and insufficient insulin secretion.
- The biguanide *metformin* is the preferred initial agent for type 2 diabetes. The primary mechanism of action of *metformin* is reduced hepatic gluconeogenesis. The drug should be avoided in severe renal impairment or acute heart failure due to the risk of lactic acidosis.
- Other agents for type 2 diabetes include sulfonylureas, meglitinides, thiazolidinediones, GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT2 inhibitors.
- Sulfonylureas (*glimepiride*, *glipizide*, *glyburide*) and meglitinides (*nateglinide*, *repaglinide*) lower glucose by enhancing secretion of insulin from β cells in the pancreas. Hypoglycemia and weight gain are common adverse effects with these agents.
- The thiazolidinediones (*pioglitazone*, *rosiglitazone*) enhance insulin sensitivity. Adverse effects include fluid retention, weight gain, and an increased risk of osteoporotic fractures. These agents are contraindicated in patients with symptomatic heart failure.
- GLP-1 receptor agonists (*dulaglutide*, *exenatide*, *liraglutide*, *lixisenatide*, *semaglutide*) improve mealtime insulin secretion, slow gastric emptying time, reduce food intake by enhancing satiety, decrease postprandial glucagon secretion, and promote β-cell proliferation. All are injectable agents. *Semaglutide* is also available in an oral formulation. The most common adverse effects are gastrointestinal (nausea, vomiting, constipation).
- DPP-4 inhibitors (*alogliptin*, *linagliptin*, *saxagliptin*, *sitagliptin*) prolong the action of incretin hormones like GLP-1, thereby increasing release of mealtime insulin and reducing inappropriate secretion of glucagon.

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- SGLT2 inhibitors (*canagliflozin*, *dapagliflozin*, *empagliflozin*, and *ertugliflozin*) reduce glucose by increasing urinary excretion of glucose. Common adverse effects with SGLT2 inhibitors are genital mycotic infections, urinary tract infections, and urinary frequency.
- Selected SGLT2 inhibitors and GLP-1 receptor agonists may have added benefits in reducing mortality or progression of coexisting disorders, such as atherosclerotic cardiovascular disease and kidney disease. SGLT2 inhibitors also have added benefit in heart failure with reduced ejection fraction.

STUDY QUESTIONS

Choose the ONE best answer.

24.1 Which of the following statements is correct regarding insulin glargine?

A. It is primarily used to control postprandial hyperglycemia.
B. It is a "peakless" insulin.
C. The prolonged duration of activity is due to slow dissociation from albumin.
D. It should not be used in a regimen with insulin lispro or glulisine.

Correct answer = B. Insulin glargine has a relatively flat, prolonged hypoglycemic effect. Because of this, it is used for basal glucose control, not postprandial. The prolonged duration is due to its low pH, which leads to precipitation at the injection site and resultant extended action. Insulin glargine is often used for basal control in a regimen where insulin lispro, glulisine, or aspart are used for mealtime glucose control. [Note: Glargine should not be combined with other insulins in the same syringe, as it may alter the pharmacodynamic properties of the medication.]

24.2 A patient with type 2 diabetes is currently being treated with insulin detemir. The physician determines that the patient needs additional insulin therapy for control of postprandial glucose. Which of the following agents is most appropriate to add at this time?

A. Insulin degludec
B. NPH insulin
C. Insulin lispro

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D. NPH/regular 70/30 insulin

Correct answer = C. Insulin lispro is a rapid-acting insulin that has an onset of action within 15 to 30 minutes. Rapid-acting insulins are administered to mimic the prandial (mealtime) release of insulin and control postprandial glucose levels. Insulin degludec is a long-acting insulin used to control fasting glucose levels. NPH insulin is an intermediate-acting insulin also used for basal (fasting) control. NPH/regular 70/30 insulin is a mixture of NPH (intermediate-acting) and regular (short-acting) insulin. The patient is already on a long-acting insulin (detemir) for basal control, and another insulin for basal control is not warranted.

24.3 A patient with type 1 diabetes is prescribed insulin glulisine as part of his diabetes regimen. How should the patient be advised to take insulin glulisine?

A. Every morning at 8 AM
B. Every night at 8 PM
C. Anytime during the day
D. 15 to 30 minutes before each meal

Correct answer = D. Insulin glulisine is a rapid-acting insulin. It works within 15 to 30 minutes of administration. The patient needs to be advised to take insulin glulisine 15 to 30 minutes before a meal to control postprandial glucose. Long-acting insulins are designed to mimic the basal insulin that the pancreas secretes throughout the day. Long-acting insulin (insulin glargine, detemir, degludec) can be taken any time of the day due to the long-acting pharmacokinetic features.

24.4 Which class of oral diabetes drugs is paired most appropriately with its primary mechanism of action?

A. DPP-4 inhibitor—inhibits breakdown of complex carbohydrates
B. SGLT2 inhibitor—increases urinary excretion of glucose
C. Sulfonylurea—increases insulin sensitivity
D. Thiazolidinedione—decreases hepatic gluconeogenesis

Correct answer = B. SGLT2 inhibitors work by inhibiting the sodium–glucose cotransporter 2 (SGLT2), resulting in decreased reabsorption of glucose in the kidney and increased urinary excretion. Sulfonylureas work primarily by increasing insulin secretion through stimulation of β cells in the pancreas. DPP-4 inhibitors work by inhibiting breakdown of incretins, thereby increasing postprandial insulin secretion

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and decreasing postprandial glucagon. TZDs work primarily by increasing insulin sensitivity.

24.5 Which of the following is the most appropriate initial oral agent for management of type 2 diabetes in patients with no other comorbid conditions?

A. Glipizide
B. Empagliflozin
C. Metformin
D. Pioglitazone

Correct answer = C. Metformin is the preferred initial agent for management of type 2 diabetes. See Figure 24.16.

24.6 Which of the following drugs for diabetes is MOST likely to cause hypoglycemia?

A. Glyburide
B. Exenatide
C. Rosiglitazone
D. Saxagliptin

Correct answer = A. Glyburide is a sulfonylurea that increases the release of insulin from the pancreatic β cells. Hypoglycemia is a common adverse effect with sulfonylureas. Both the GLP-1 receptor agonist exenatide and the DPP-4 inhibitor saxagliptin increase insulin release in response to meals, but the risk of hypoglycemia is much lower with these agents. The TZD rosiglitazone does not increase release of insulin.

24.7 A 56-year-old man with type 2 diabetes recently experienced a myocardial infarction (heart attack). He takes metformin and canagliflozin for his diabetes, and his A1c is still above goal. Which of the following drugs is most appropriate to initiate for this patient?

A. Glipizide
B. Liraglutide
C. Pioglitazone
D. Sitagliptin

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Correct answer = B. Liraglutide is a GLP-1 receptor agonist that is also approved to reduce the risk of cardiovascular mortality in patients with type 2 diabetes and cardiovascular disease. Given the patient's recent myocardial infarction, this is the most appropriate agent. The other choices listed do not have evidence of improved cardiovascular outcomes in patients with diabetes and cardiovascular disease.

24.8 A patient with newly diagnosed type 2 diabetes has severe chronic kidney disease (estimated glomerular filtration rate less than 30 mL/min/1.73 m^2). Which of the following oral agents for diabetes is most appropriate for this patient?

A. Dapagliflozin
B. Glyburide
C. Linagliptin
D. Metformin

Correct answer = C. Linagliptin is a DPP-4 inhibitor that does not require dosing adjustment in renal dysfunction. Although the SGLT2 inhibitor dapagliflozin is indicated to reduce the risk of end-stage kidney disease, the clinical efficacy of the SGLT2 inhibitors declines with reduced renal function. SGLT2 inhibitors are contraindicated in patients with severe renal impairment. The risk of hypoglycemia increases with use of glyburide in renal dysfunction, and this agent should be avoided. Metformin should be avoided in severe renal impairment due to the risk of lactic acidosis.

24.9 Which of the following combinations of drugs for type 2 diabetes has an overlapping mechanism of action?

A. Glipizide–repaglinide
B. Metformin–empagliflozin
C. Metformin–semaglutide
D. Sitagliptin–pioglitazone

Correct answer = A. The sulfonylurea glipizide and the meglitinide repaglinide both increase secretion of insulin from the β cells of the pancreas. Concurrent use of sulfonylureas and meglitinides should be avoided due to the increased risk of hypoglycemia. The other combinations do not have overlapping mechanisms of action. Of note, the combination of DPP-4 inhibitors and GLP-1 receptor agonists is another combination that should be avoided for management of type 2 diabetes due to overlapping mechanisms of action and increased potential for toxicity.

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24.140 A 67-year-old woman with type 2 diabetes also has heart failure with reduced ejection fraction (HFrEF). She takes metformin for diabetes, and she has mild renal impairment. Which of the following may be beneficial to assist with management of both her diabetes and HFrEF?

A. Dapagliflozin
B. Exenatide
C. Nateglinide
D. Saxagliptin

Correct answer = A. Dapagliflozin is indicated for the treatment of type 2 diabetes, as well as the treatment of HFrEF. The other agents do not have an indication for HFrEF, and the DPP-4 inhibitor saxagliptin may increase the risk of heart failure hospitalizations.

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25

Estrogens, Progestogens, and Androgens

Karen L. Whalen, Stacy L. Miller

I. OVERVIEW

Estrogens, androgens, and progesterone are sex hormones produced by the gonads (the ovaries in females and the testes in males). Sex hormones are synthesized from the precursor, cholesterol, in a series of steps that includes shortening of the hydrocarbon side chain and hydroxylation of the steroid nucleus. These hormones are important for conception, embryonic maturation, and development of primary and secondary sexual characteristics at puberty. The sex hormones and their synthetic derivatives are used therapeutically for contraception, management of menopausal symptoms, and replacement therapy in hormone deficiency. Several antagonists are effective in the treatment or prevention of hormone-responsive cancers. Figure 25.1 lists the estrogens and progestogens discussed in this chapter.

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ESTROGENS

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Conjugated estrogens PREMARIN
Esterified estrogens MENEST
Estradiol **(oral)** ESTRACE
Estradiol **(topical)** DIVIGEL, ESTROGEL
Estradiol **(transdermal)** ALORA, CLIMARA, VIVELLE

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VIVELLE

***Estradiol* (vaginal)** ESTRACE, ESTRING, FEMRING, VAGIFEM

***Estradiol* (vaginal cream)** ESTRACE

***Estradiol* (vaginal insert)** VAGIFEM

***Estradiol* (vaginal ring)** ESTRING, FEMRING

Estropipate GENERIC ONLY

Ethinyl estradiol*

SELECTIVE ESTROGEN-RECEPTOR MODULATORS (SERMs)

***Bazedoxifene* (with CEE)** DUAVEE

Clomiphene CLOMID

Ospemifene OSPHENA

Raloxifene EVISTA

Tamoxifen GENERIC ONLY

PROGESTOGENS**

***Desogestrel* (with EE)** GENERIC ONLY

***Dienogest* (with EV)** NATAZIA

Drospirenone SLYND

***Drospirenone* (with E)** ANGELIQ

***Drospirenone* (with EE)** YASMIN, YAZ

***Etonogestrel* (subdermal)** NEXPLANON

***Etonogestrel* (with EE – vaginal ring)** NUVARING

***Levonorgestrel* (oral)** PLAN B ONE-STEP

***Levonorgestrel* (IUD)** KYLEENA, LILETTA, MIRENA, SKYLA

***Levonorgestrel* (with E – transdermal)** CLIMARA PRO

***Levonorgestrel* (with EE – oral)**

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Figure 25.1 Summary of estrogens and progestogens.*Available in combination with various progestins. **Progestogens that are designated as available in combination with *ethinyl estradiol* or *estradiol valerate* are used as contraceptive agents. Those listed in combination with *conjugated equine estrogens* or *estradiol* are used for hormone therapy. CEE = *conjugated equine estrogens*; E = *estradiol;* EE = *ethinyl estradiol*; EV = *estradiol valerate;* IUD = intrauterine device.

II. ESTROGENS

Estradiol [ess-tra-DYE-ole] is the most potent estrogen produced and secreted by the ovary. It is the principal estrogen in premenopausal

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women. *Estrone* [ESS-trone] is both a precursor and a metabolite of *estradiol*, and it has approximately one-third the estrogenic potency of *estradiol. Estrone* is the primary circulating estrogen after menopause, where it is generated mainly from conversion of dehydroepiandrosterone (DHEA) in adipose tissue. *Estriol* [ess-TRI-ole], another metabolite of *estradiol*, is significantly less potent than is *estradiol.* It is present in significant amounts during pregnancy, because it is synthesized by the placenta. Synthetic estrogens, such as *ethinyl estradiol* [ETH-ih-nil ess-tra-DYE-ole], undergo less first-pass metabolism than do naturally occurring hormones and, thus, are effective when administered orally at lower doses.

A. Mechanism of action

After dissociation from their binding sites on sex hormone–binding globulin or albumin in the plasma, steroid hormones (for example, *estradiol*) diffuse across the cell membrane and bind with high affinity to specific nuclear receptor proteins (Figure 25.2). The activated steroid–receptor complex interacts with nuclear chromatin to initiate hormone-specific RNA synthesis. This results in the synthesis of specific proteins that mediate a number of physiologic functions. [Note: The steroid hormones may elicit the synthesis of different RNA species in diverse target tissues and, therefore, are both receptor and tissue specific.] Other pathways that require these hormones have been identified that lead to more rapid actions.

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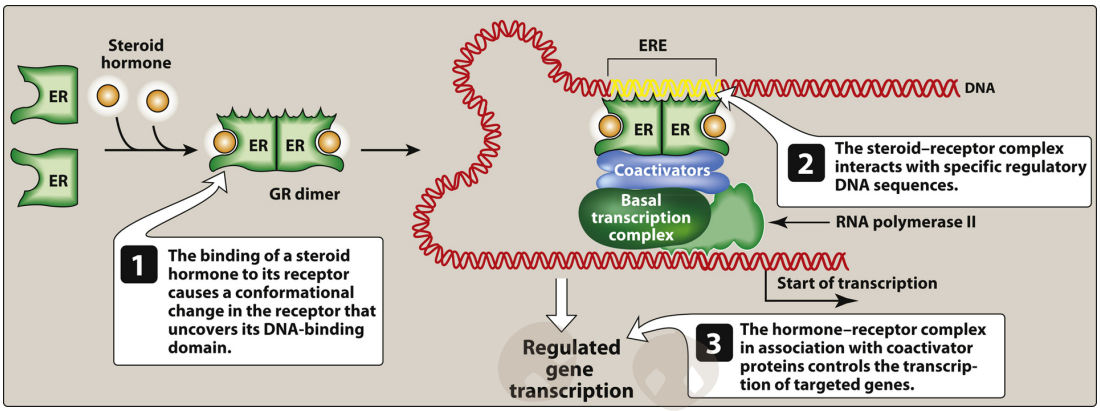

Figure 25.2 Transcriptional regulation by intracellular steroid hormone receptors.ER = estrogen receptor; ERE = estrogen response element; GR = glucocorticoid receptor.

B. Therapeutic uses

Estrogens are most frequently used for contraception and menopausal hormone therapy (HT). In the past, estrogens were widely used for prevention of osteoporosis; however, due to risks associated with estrogen therapy, current guidelines recommend use of other therapies, such as bisphosphonates (see Chapter 27).

1.Contraception: The combination of an estrogen and progestogen provides effective contraception via the oral, transdermal, or vaginal route.

2.Menopausal hormone therapy: Declining levels of estrogen after menopause trigger menopausal symptoms, such as vasomotor instability (for example, “hot flashes” or “hot flushes”) and vaginal atrophy (Figure 25.3). The primary indication for estrogen therapy in menopausal women is management of moderate to severe vasomotor symptoms. Oral, transdermal, and topical preparations of *estradiol* are effective in treating vasomotor symptoms, as well as urogenital symptoms associated with menopause. Another common oral preparation used for the treatment of menopausal symptoms is *conjugated equine estrogens* (obtained from urine of pregnant mares), which primarily contains sulfate esters of *estrone* and *equilin.* Other *estrone*-based oral preparations include *esterified estrogens* and *estropipate* [ES-

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troe-PIP-ate]. For women with an intact uterus, a progestogen should be included with oral, transdermal, or topical estrogen therapy, because the progestogen reduces the risk of endometrial carcinoma associated with unopposed estrogen. [Note: Some vaginal ring formulations of estrogen therapy obtain high enough systemic levels that addition of a progestin is warranted.] Women who have undergone a hysterectomy may use estrogen-based preparations alone for HT. [Note: The potency of estrogen used in HT is substantially less than that of estrogens used in contraception. Thus, the adverse effects of estrogen associated with HT are usually less than those seen in women taking estrogen for contraceptive purposes.] Use of HT has been associated with an increased risk of cardiovascular events and breast cancer. Thus, HT should be prescribed at the lowest effective dose to relieve menopausal symptoms. Postmenopausal women who have only localized urogenital symptoms, such as vaginal atrophy and dyspareunia, should be treated with vaginal formulations rather than systemic estrogen to minimize the risks of use. [Note: Vaginal formulations of estrogen formulated specifically to treat local urogenital symptoms of menopause include vaginal creams, inserts, and the lower-dose vaginal ring.]

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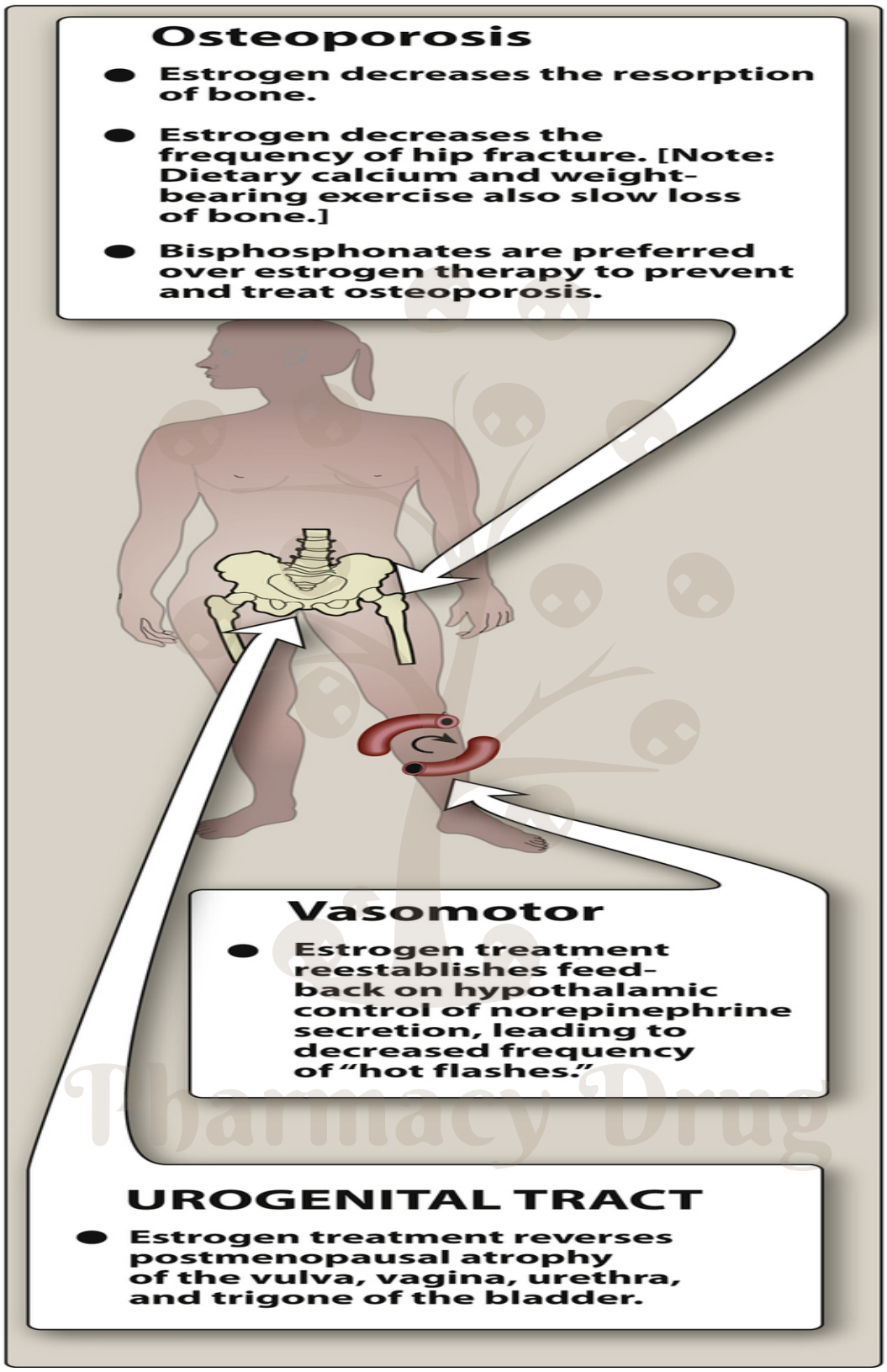

Figure 25.3 Benefits associated with postmenopausal estrogen replacement.

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Clinical Application 25.1: Diagnosis of Menopause and Management of Menopausal Symptoms

Menopause is defined as the cessation of menses. It is diagnosed after 12 months of amenorrhea (absence of menstrual cycles) in women who do not have another biologic reason for cessation of menses. Elevated levels of follicle-stimulating hormone (FSH) may also support the diagnosis of menopause but are not necessary for confirmation. The average age of menopause in the United States is 51 years, but this may vary depending on the region of the world. The majority of women reach menopause between the ages of 45 and 55.

In the few years before menopause (perimenopausal period), and after menopause, declining levels of estrogen occur due to the loss of ovarian function. Lower levels of estrogen contribute to menopausal symptoms, such as vasomotor instability (hot flashes and night sweats), vaginal dryness and atrophy, sleep disturbances, and mood changes. Women who have moderate to severe vasomotor symptoms that are affecting quality of life should be prescribed hormone therapy to alleviate symptoms. Hormone therapy is available in a variety of formulations (oral, topical, transdermal, and vaginal), and patient preference for route of administration should be considered. The lowest dose of estrogen that successfully manages vasomotor and other symptoms should be used. Women who have an intact uterus must use a progestin along with the estrogen therapy to reduce the risk of endometrial hyperplasia and carcinoma associated with estrogen use. The duration of hormone therapy for menopausal symptoms should be individualized, with periodic tapering of the drug therapy to see if symptoms recur. For women who are not candidates for hormone therapy, alternatives for management of vasomotor symptoms include selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, and *gabapentin.* Women who have only localized urogenital symptoms should be treated with vaginal formulations rather than systemic estrogen to minimize the risks of use.

3.Other uses: Estrogen therapy mimicking the natural cyclic pattern, and usually in combination with a progestogen, is instituted to stimulate development of secondary sex

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characteristics in young women with primary hypogonadism. Similarly, replacement therapy is used for women who have hormonal deficiencies due to surgical menopause or premature ovarian failure. Estrogen is also used as a feminizing hormone therapy in patients with gender dysphoria and transgender patients undergoing the gender transition process.

C. Pharmacokinetics

1.Naturally occurring estrogens: These agents and their esterified or conjugated derivatives are readily absorbed through the gastrointestinal tract, skin, and mucous membranes. Taken orally, *estradiol* is rapidly metabolized (and partially inactivated) by the microsomal enzymes of the liver. Micronized *estradiol* has better bioavailability. Although *estradiol* is subject to first-pass metabolism, it is still effective when taken orally.

2.Synthetic estrogens: These compounds, such as *ethinyl estradiol* and *estradiol valerate,* are well absorbed after oral administration. *Estradiol valerate* is a prodrug of *estradiol* that is rapidly cleaved to *estradiol* and valeric acid. The synthetic estrogens are fat soluble, stored in adipose tissue, and slowly released. These compounds have a prolonged action and a higher potency compared with the natural estrogens.

3.Metabolism: Bioavailability of *estradiol* after oral administration is low due to first-pass metabolism. To reduce first-pass metabolism, *estradiol* may be administered via a transdermal patch, topical formulation (gel or spray), intravaginal preparation (tablet, cream, or ring), or injection. Following oral administration, *estradiol* is metabolized to *estrone* and *estriol.* Estrogens are transported in the blood bound to serum albumin or sex hormone–binding globulin. *Estradiol* and its metabolites subsequently undergo glucuronide and sulfate conjugation. In addition, smaller amounts of *estrone* and *estriol* are metabolized by the hepatic CYP3A4 isoenzyme. Metabolites are mainly excreted in the urine. The glucuronide and sulfate metabolites are also subject to enterohepatic recirculation. These metabolites are secreted into the bile, hydrolyzed by gut bacteria, and then reabsorbed.

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D. Adverse effects

Nausea and breast tenderness are among the most common adverse effects of estrogen therapy. In addition, the risk of thromboembolic events, myocardial infarction, and breast and endometrial cancer is increased with the use of estrogen therapy. [Note: The increased risk of endometrial cancer can be offset by including a progestogen along with the estrogen therapy.] Other effects of estrogen therapy are shown in Figure 25.4.

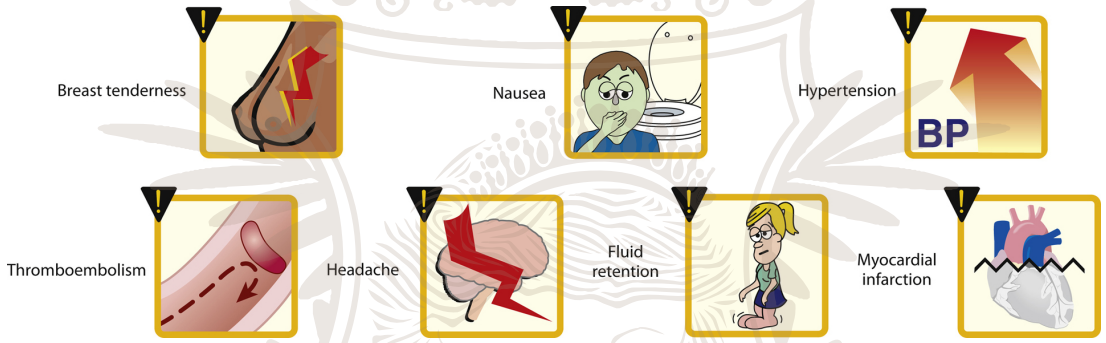

Figure 25.4 Some adverse effects associated with estrogen therapy.BP = blood pressure.

III. SELECTIVE ESTROGEN RECEPTOR MODULATORS

Selective estrogen receptor modulators (SERMs) are a class of estrogen-related compounds that display selective agonism or antagonism for estrogen receptors depending on the tissue type. This category includes *tamoxifen*, *raloxifene*, *bazedoxifene*, *clomiphene*, and *ospemifene*.

A. Mechanism of action

Tamoxifen [tah-MOKS-ih-fen] and *raloxifene* [rah-LOX-ih-feen] compete with estrogen for binding to the estrogen receptor in breast tissue. [Note: Normal breast growth is stimulated by estrogens. Therefore, some hormone-responsive breast tumors regress following treatment with these agents.] In addition, *raloxifene* acts as an

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estrogen agonist in bone, leading to decreased bone resorption, increased bone density, and decreased vertebral fractures (Figure 25.5). Unlike estrogen and *tamoxifen*, *raloxifene* does not stimulate growth of the endometrium and, therefore, does not predispose to endometrial cancer. *Raloxifene* also lowers serum total cholesterol and low-density lipoprotein (LDL). Like *raloxifene*, *bazedoxifene* [BA-ze-DOX-i-feen] antagonizes the action of estrogen on the uterus. The drug reduces the risk of endometrial hyperplasia with estrogen use. *Clomiphene* [KLOE-mi-feen] acts as a partial estrogen agonist and interferes with the negative feedback of estrogens on the hypothalamus. This effect increases the secretion of gonadotropin-releasing hormone and gonadotropins, thereby leading to stimulation of ovulation.

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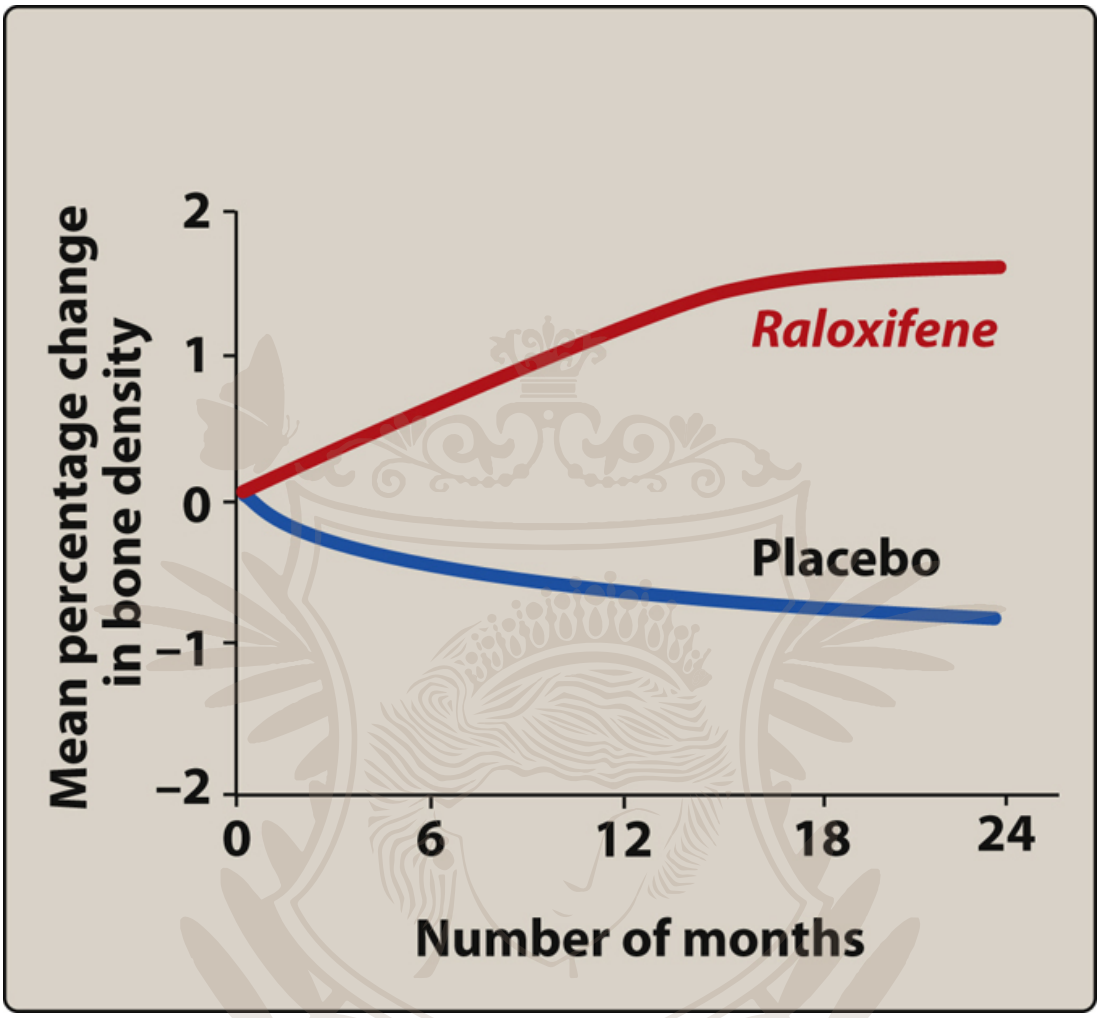

Figure 25.5 Hip bone density increases with *raloxifene* in postmenopausal women.

B. Therapeutic uses

Tamoxifen is currently used in the treatment of metastatic breast cancer or as adjuvant therapy following mastectomy or radiation for breast cancer. Both *tamoxifen* and *raloxifene* can be used as prophylactic therapy to reduce the risk of breast cancer in high-risk patients. *Raloxifene* is also approved for the prevention and treatment of osteoporosis in postmenopausal women, although other agents such as bisphosphonates are preferred for this indication. *Clomiphene* is used in the treatment of infertility. *Ospemifene* is indicated for the treatment of dyspareunia (painful sexual intercourse) related to menopause. *Bazedoxifene* is available in a combination product with

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conjugated equine estrogens. The combination is indicated for the treatment of menopausal symptoms in women with an intact uterus.

C. Pharmacokinetics

The SERMs are rapidly absorbed after oral administration. *Tamoxifen* is extensively metabolized by the cytochrome P450 system, including the formation of active metabolites via the CYP3A4 and CYP2D6 isoenzymes. [Note: Patients with a genetic polymorphism may be poor CYP2D6 metabolizers and produce less active metabolite, resulting in diminished activity of *tamoxifen*.] *Raloxifene* is rapidly converted to glucuronide conjugates through first-pass metabolism. These agents undergo enterohepatic cycling, and the primary route of excretion is through the bile into feces.

D. Adverse effects

The most frequent adverse effects of *tamoxifen* are hot flashes and nausea. Due to its estrogenic activity in the endometrium, endometrial hyperplasia and malignancies have been reported with *tamoxifen* therapy. Risks of *tamoxifen* should be reviewed with patients before initiation of drug therapy. Because it is metabolized by various CYP450 isoenzymes, *tamoxifen* is subject to many drug interactions. *Tamoxifen* has been associated with QT prolongation, and concurrent use of other agents that prolong the QT interval (for example, *amiodarone*, *clarithromycin*, and *trazodone*) should be avoided if possible. Hot flashes and leg cramps are common adverse effects with *raloxifene.* In addition, there is an increased risk of deep vein thrombosis and pulmonary embolism. Women who have a past or active history of venous thromboembolic events should not take the drug. Adverse effects of *clomiphene* are dose related and include headache, nausea, vasomotor flushes, visual disturbances, and ovarian enlargement. Use of *clomiphene* increases the risk of multiple gestation, usually twins. *Ospemifene* may stimulate endometrial growth, and addition of a progestogen in women with an intact uterus should be considered.

IV. PROGESTOGENS

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Progesterone, the natural progestogen, is produced in response to luteinizing hormone (LH) by both females (secreted by the corpus luteum, primarily during the second half of the menstrual cycle, and by the placenta) and males (secreted by the testes). It is also synthesized by the adrenal cortex in both sexes.

A. Mechanism of action

Progestogens exert their effects in a manner analogous to that of the other steroid hormones. In females, progesterone promotes the development of a secretory endometrium that can accommodate implantation of a newly forming embryo. The high levels of progesterone that are released by the corpus luteum during the second half of the menstrual cycle (the luteal phase) inhibit the production of gonadotropins and, therefore, prevent further ovulation. If conception takes place, progesterone continues to be secreted, maintaining the endometrium in a favorable state for the continuation of the pregnancy and reducing uterine contractions. If conception does not take place, the corpus luteum regresses, and the release of progesterone ceases abruptly. The decline in progesterone stimulates the onset of menstruation. Figure 25.6 summarizes the hormones produced during the menstrual cycle.

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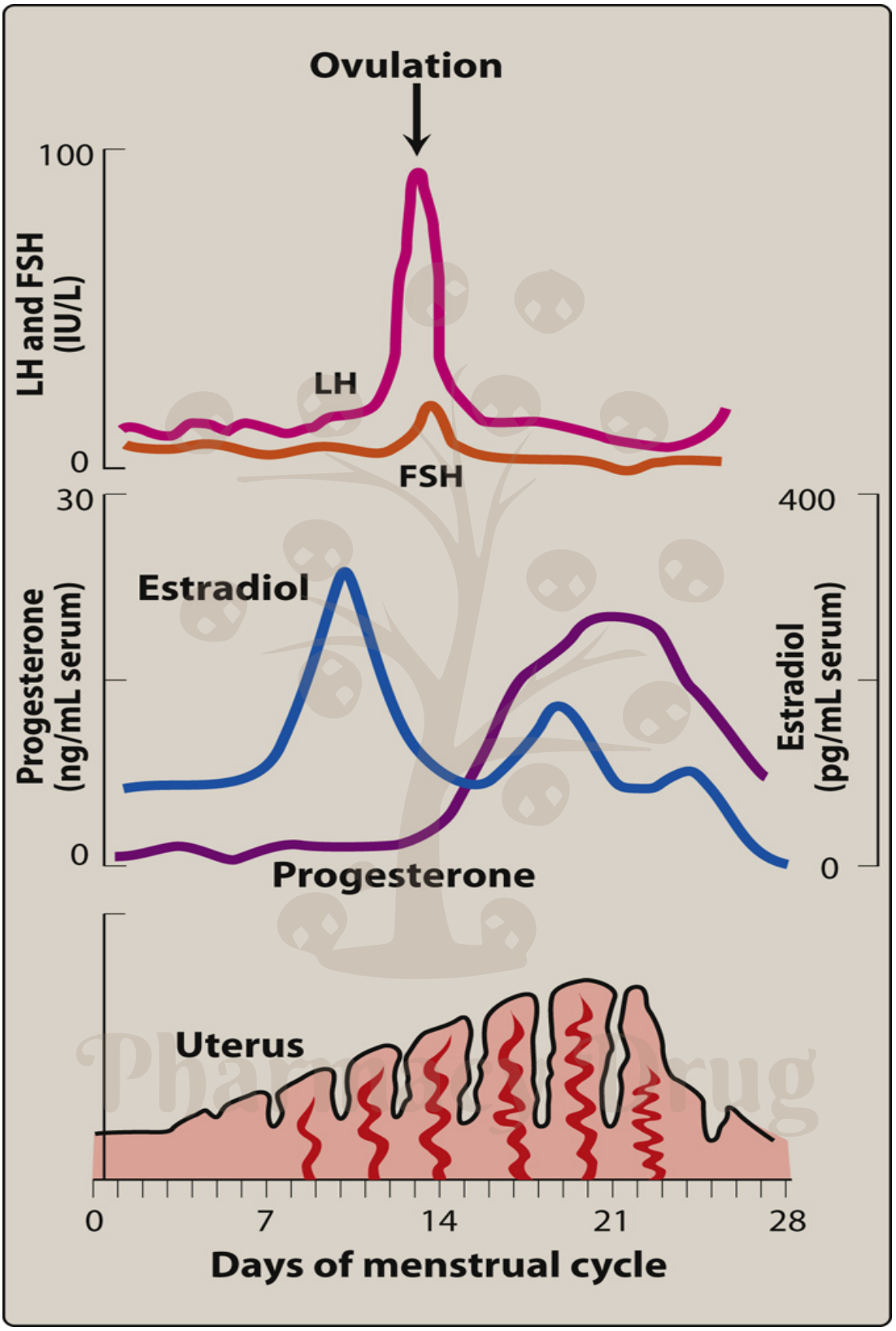

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Figure 25.6 The menstrual cycle with plasma levels of pituitary and ovarian hormones and a schematic representation of changes in the morphology of the uterine lining.FSH = follicle-stimulating hormone; LH = luteinizing hormone.

B. Therapeutic uses

The major clinical uses of progestogens are for contraception or menopausal hormone therapy. For both contraception and HT, progestogens are often used in combination with estrogens. Progesterone is not used as a contraceptive therapy because of its rapid metabolism, resulting in low bioavailability. Synthetic progestogens (that is, progestins) used for contraception are more stable to first-pass metabolism, allowing lower doses when administered orally. These agents include *desogestrel* [des-oh-JES-trel], *dienogest* [dye-EN-oh-jest], *drospirenone* [droe-SPY-re-none], *levonorgestrel* [lee-voe-nor-JES-trel], *norethindrone* [nor-ETH-in-drone], *norethindrone acetate*, and *norgestimate* [nor-JES-tih-mate]. *Medroxyprogesterone* [me-DROK-see-proe-JES-ter-one] *acetate* is an injectable contraceptive, and the oral form is a common progestin component of menopausal HT. Progestogens are also used for the control of heavy menstrual bleeding, treatment of dysmenorrhea, and management of endometriosis and infertility.

C. Pharmacokinetics

A micronized preparation of *progesterone* is rapidly absorbed after oral administration. It has a short half-life in the plasma and is metabolized by the liver to pregnanediol and glucuronide and sulfate conjugates. The metabolites are excreted primarily in the urine. Synthetic progestins are less rapidly metabolized. Oral *medroxyprogesterone acetate* has a half-life of 16 to 30 hours. When injected intramuscularly or subcutaneously, the drug has a half-life of about 40 to 50 days and provides contraception for approximately 3 months. The other progestins have half-lives of 7 to 30 hours, allowing for once-daily dosing.

D. Adverse effects

The major adverse effects associated with the use of progestins are headache, depression, weight gain, and changes in libido (Figure

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25.7). Progestins that are derived from 19-nortestosterone (for example, *norethindrone*, *norethindrone acetate*, *levonorgestrel*) possess some androgenic activity because of their structural similarity to *testosterone* and can cause acne and hirsutism. Less androgenic progestins, such as *norgestimate* and *drospirenone*, may be preferred in women with acne. *Drospirenone*, an analog of *spironolactone*, can raise serum potassium due to antimineralocorticoid effects, and concurrent use with other drugs that increase potassium (for example, angiotensin-converting enzyme inhibitors) may increase the risk of hyperkalemia.

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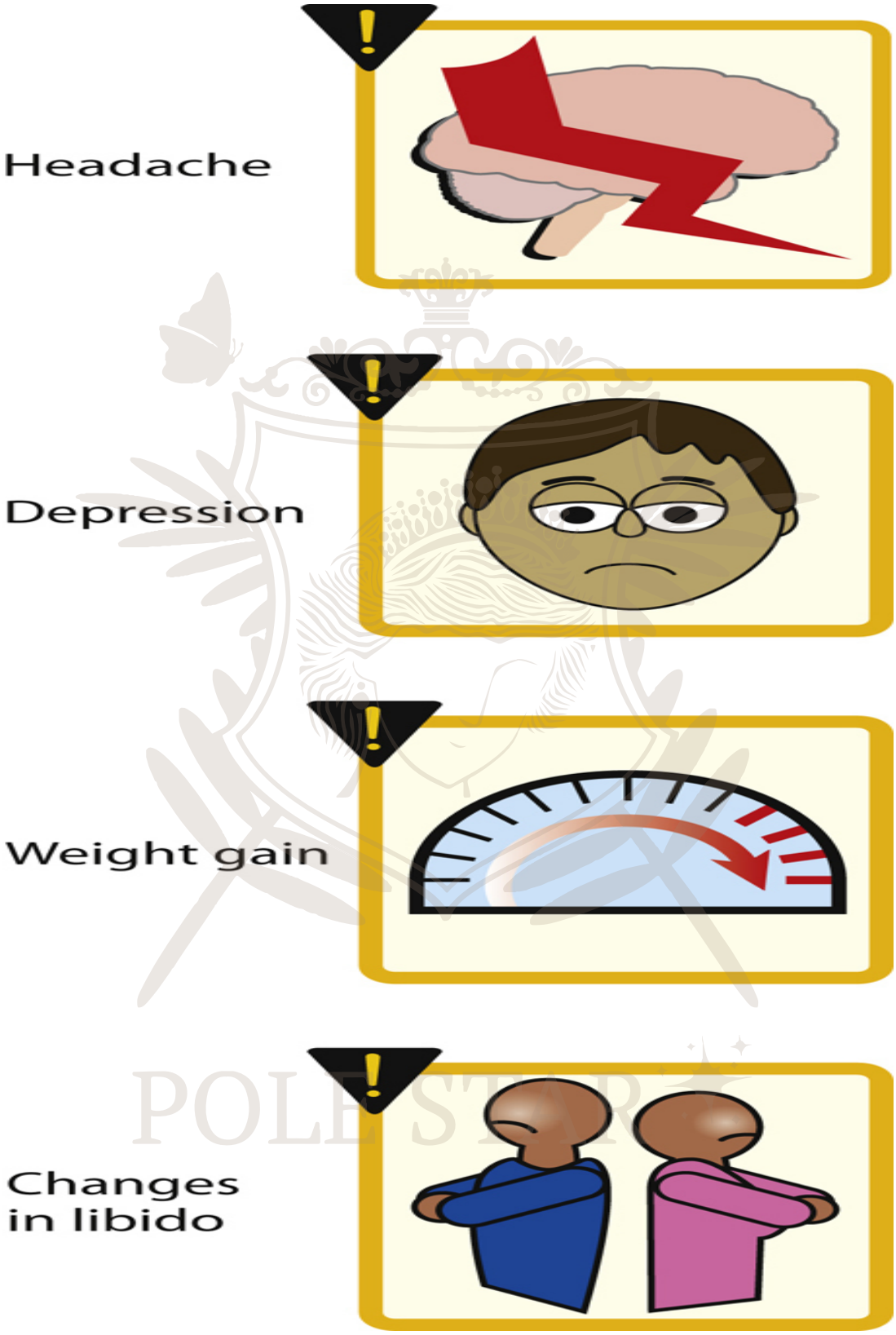

Figure 25.7 Some adverse effects associated with progestin therapy.

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E. Progesterone antagonist

Mifepristone [mih-feh-PRIH-stone] (also designated as RU-486) is a progesterone antagonist. Administration of this drug results in termination of pregnancy due to interference with the progesterone needed to maintain pregnancy. *Mifepristone* is often combined with the prostaglandin analog *misoprostol* to induce uterine contractions. The major adverse effects are abdominal pain, uterine bleeding, and the possibility of incomplete termination of pregnancy.

V. CONTRACEPTIVES

Contraceptives may be hormonal or nonhormonal (for example, condom, diaphragm, contraceptive sponge, and copper intrauterine device [IUD]). Hormonal contraceptives may be classified as combination hormonal contraceptives (combination of estrogen and a progestin—combination oral contraceptives, transdermal patch, and vaginal ring) or progestin-only contraceptives (progestin-only pills, injectable, implant, or IUD). Figure 25.8 outlines the frequency of use for various hormonal and nonhormonal methods of contraception. An overview of the hormonal methods of contraception is provided below.

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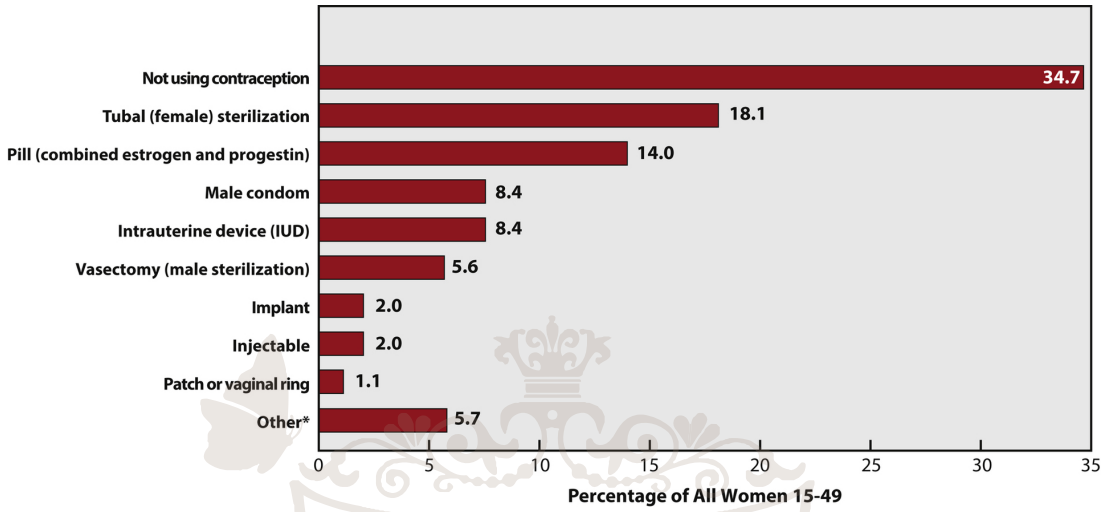

Figure 25.8 Comparison of contraceptive use among US women ages 15 to 49 years.*Withdrawal fertility awareness methods, and other barrier methods (for example, diaphragm).Data from Current Contraceptive Status Among Women Aged 15–49; United States, 2017–2019, Available at https://www.cdc.gov/nchs/products/databriefs/db388.htm.

A. Types of hormonal contraceptives

1.Combination oral contraceptives: Combination oral contraceptives (COCs) contain a combination of estrogen, most often *ethinyl estradiol*, and a progestin. These preparations are highly effective in achieving contraception (Figure 25.9). Monophasic COCs contain a constant dose of estrogen and progestin in each pill. Triphasic oral contraceptive products attempt to mimic the natural female cycle and usually contain a constant dose of estrogen with increasing doses of progestin. With most COCs, active hormone-containing pills are administered for 21 to 24 days, followed by 4 to 7 days of placebo pills, for a total regimen of 28 days in each pill pack. Withdrawal bleeding occurs during the hormone-free (placebo) interval. One four-phasic product contains varying doses of *estradiol valerate* and *dienogest* throughout the 28-day cycle, with only 2 placebo days. Use of extended-cycle contraception (84 active pills followed by 7 days of placebo) results in less frequent withdrawal bleeding. A continuous oral contraceptive product (active pills taken every day) is also available.

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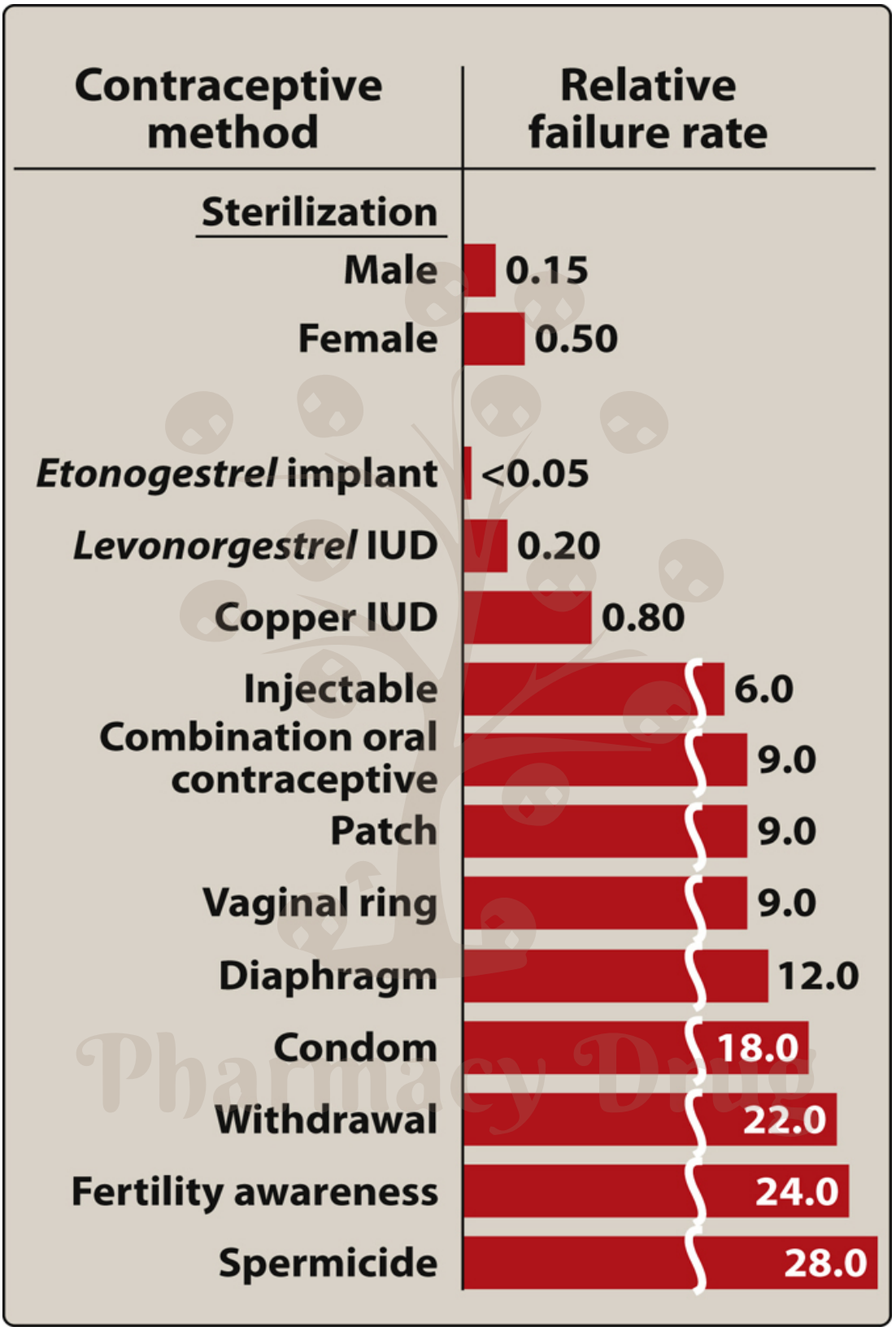

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Figure 25.9 Comparison of failure rate for various methods of contraception with typical use.Longer bars indicate a higher failure rate—that is, more pregnancies.

2.Transdermal patch: The transdermal contraceptive patch contains a combination of *ethinyl estradiol* with a progestin, either *norelgestromin* or *levonorgestrel.* During the 28-day cycle, one patch is applied once weekly for 3 weeks to the abdomen, upper torso, or buttock. Each patch is worn for 1 week and then removed. No patch is worn during the fourth week, and withdrawal bleeding occurs. The transdermal patch has efficacy comparable with that of the oral contraceptives, but it is less effective in women weighing greater than 90 kg. Total estrogen exposure with the transdermal contraceptive patch may be significantly greater than that seen with oral contraceptives, leading to an increased risk of venous thromboembolism. The risk of thromboembolism may be higher in women with a body mass index ≥ 30 kg/m^2, and use of the transdermal contraceptive patch is contraindicated in these patients.

3.Vaginal ring: The contraceptive vaginal ring contains *ethinyl estradiol* and *etonogestrel.* The ring is inserted into the vagina and left in place for 3 weeks. After 3 weeks, the ring is removed, and withdrawal bleeding occurs during the fourth week. The most common reason for discontinuation of this product is device related (for example, vaginal irritation or device expulsion).

4.Progestin-only pills: Progestin-only pills (the “mini-pill”) usually contain *norethindrone* and are administered daily to deliver a low, continuous dosage of drug. These preparations are less effective than combination oral contraceptives, and irregular menstrual cycles may be more frequent. An alternative progestin-only pill with *drospirenone* provides 24 days of active hormone and 4 days of placebo per 28-day cycle. Progestin-only pills may be used in patients who are breastfeeding or those who have intolerance or contraindications to estrogen-containing products. [Note: Estrogen can bind to prolactin receptors and reduce milk

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production in breastfeeding mothers. Unlike estrogen, progestins do not affect milk production.]

5.Injectable progestin: *Medroxyprogesterone acetate* is a contraceptive that is administered via intramuscular or subcutaneous injection every 3 months. This product provides high sustained levels of progestin, and many women experience amenorrhea with *medroxyprogesterone acetate.* In addition, return to fertility may be delayed for several months after discontinuation. Weight gain is a common adverse effect. *Medroxyprogesterone acetate* may contribute to bone loss and predispose patients to osteoporosis and/or fractures. Therefore, the drug should not be continued for more than 2 years unless other methods of contraception are inappropriate for the patient.

6.Progestin implant: After subdermal placement in the upper arm, the *etonogestrel* implant offers contraception for up to 3 years. The implant is as reliable as sterilization, and the contraceptive effect is reversible when removed. [Note: Progestin implants and intrauterine devices are known as long-acting reversible contraceptives (LARC). LARC methods are the most effective contraceptives, since efficacy is not reliant on patient adherence.] Adverse effects include irregular menstrual bleeding and headaches. The *etonogestrel* implant has not been studied in women who weigh more than 130% of ideal body weight and may be less effective in this population.

7.Progestin intrauterine device: Several *levonorgestrel*-releasing intrauterine devices are available, providing a highly effective method of contraception for 3 to 7 years. This is a suitable method of contraception for women who desire long-term contraception. It should be avoided in patients with pelvic inflammatory disease or a history of ectopic pregnancy. The *levonorgestrel* IUD is a highly effective treatment for heavy menstrual bleeding. [Note: The nonhormonal copper IUD provides contraception for up to 10 years. In contrast to the *levonorgestrel* IUD, the copper IUD can increase menstrual bleeding.]

8.Postcoital contraception: Postcoital or emergency contraception reduces the probability of pregnancy after

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intercourse without effective contraception (Figure 25.10) to between 0.2% and 3%. The most common method of emergency contraception uses a single high dose of *levonorgestrel.* For maximum effectiveness, emergency contraception should be taken as soon as possible after unprotected intercourse and preferably within 72 hours. The *levonorgestrel* emergency contraceptive regimens are generally better tolerated than the estrogen–progestin combination regimens. An alternative emergency contraceptive is the progesterone agonist/antagonist *ulipristal* [ue-li-PRIS-tal]. It is indicated for emergency contraception within 5 days of unprotected intercourse. [Note: Insertion of the copper intrauterine device within 5 days of unprotected intercourse is another method of emergency contraception, and it also provides long-term contraception.]

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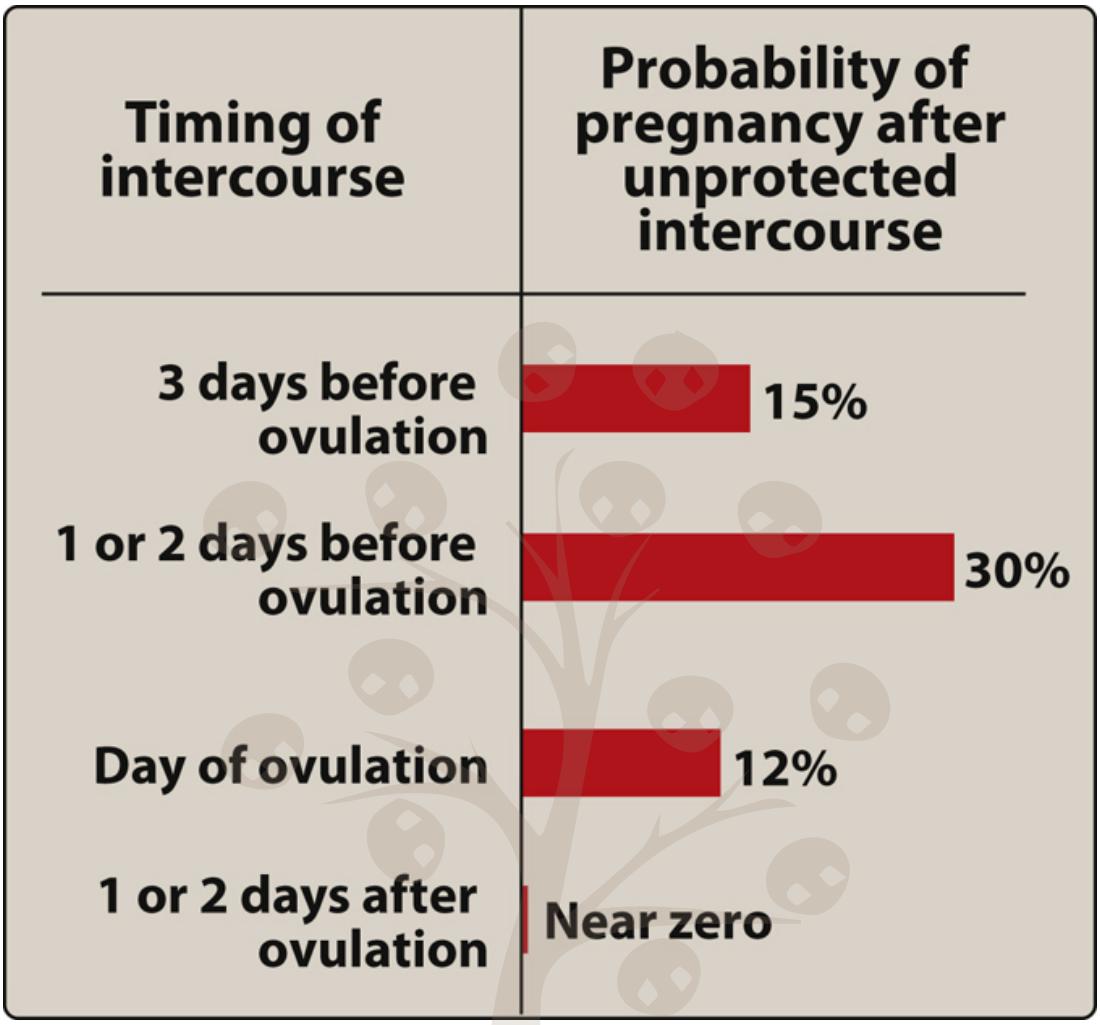

Figure 25.10 Risk of pregnancy after unprotected intercourse in young couples in their mid-twenties.

Clinical Application 25.2: Selection of a Contraceptive Method

Given the wide variety of available contraceptives, the task of selecting a contraceptive agent for a patient may seem challenging. Using the series of questions below to collect information from the patient and the medical record will help refine the choices and guide the clinician to the selection of an appropriate contraceptive agent.

1. Is the patient amenable to the use of hormonal contraception? If the patient does not want to use hormones, a nonhormonal form of contraception (for example, condom, diaphragm, copper intrauterine device, or fertility awareness methods) should be recommended.

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2. Does the patient have contraindications to estrogen, such as advanced age, thromboembolic disease, or cigarette smoking? Contraindications to estrogen should guide the clinician to the use of progestin-only products (for example, the progestin-only pill, injectable, implant, or *levonorgestrel* IUD) or nonhormonal methods of contraception.
3. What other health conditions does the patient have that might influence the choice of contraceptive agent? If clinicians are uncertain about contraceptives that are acceptable for use with concurrent medical conditions, they should consult a medical reference. An example of a useful reference chart to guide selection of contraceptives is the CDC Summary Chart of US Medical Eligibility Criteria for Contraceptive Use https://www.cdc.gov/reproductivehealth/contraception/pdf/summary-chart-us-medical-eligibility-criteria_508tagged.pdf.
4. What is the expected duration of contraceptive therapy? If patients are seeking long-term contraception, a LARC method such as the IUD or implant is an excellent choice. For patients who only need short-term contraception, the LARC methods are not the most appropriate.
5. What is the patient preference for type of contraceptive therapy? Does the patient prefer pills, patches, IUD, etc.? This information will help guide selection of a contraceptive agent.
6. What is the ability to adhere to therapy? For patients who have difficulty remembering to take a pill each day, change a patch each week, etc., a LARC method should be considered. LARC methods have the highest efficacy rate, since they are not reliant on the patient for adherence.

B. Mechanism of action

Exogenously administered estrogen in contraceptives provides negative feedback that blunts release of FSH by the pituitary gland, and progestin inhibits LH secretion, thus preventing ovulation. Progestin also thickens the cervical mucus, thus hindering the ability of sperm to reach the ovum. Withdrawal of the progestin (for example, during the placebo pill week, or week without patch or ring during each 28-day cycle) stimulates withdrawal bleeding.

C. Adverse effects

Adverse effects associated with various contraceptives are determined by the specific estrogen and progestin compounds in the product. The most common adverse effects with estrogens are breast fullness, fluid retention, headache, and nausea. Increased blood pressure may also occur. Progestins may be associated with

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depression, changes in libido, hirsutism, and acne. Although rare, thromboembolism, thrombophlebitis, myocardial infarction, and stroke may occur with use of estrogen-containing contraceptives. These severe adverse effects are most common among women who are over age 35 years and smoke, and estrogen-containing contraceptives should be avoided in this population. Progestin-only products are preferred in older women who are smokers, due to a lower risk of severe adverse effects. Breakthrough bleeding is a common adverse effect of COCs and progestin-only pills. This adverse effect is more likely with new users and those on lower-dose pills. The incidence of cervical cancer may be increased with hormonal contraceptives, because women are less likely to use barrier methods of contraception that reduce exposure to human papillomavirus, the primary risk factor for cervical cancer. [Note: Oral contraceptives are associated with a decreased risk of endometrial and ovarian cancer.] Oral contraceptives are contraindicated in the presence of cerebrovascular and thromboembolic disease, estrogen-dependent neoplasms, liver disease, and pregnancy. Drugs that induce the CYP3A4 isoenzyme (for example, *rifampin*, *carbamazepine*, and *phenytoin*) significantly reduce the efficacy of oral contraceptives. Concurrent use of these agents with oral contraceptives should be avoided, or an alternate barrier method of contraception should be utilized. Antibiotics that alter normal gastrointestinal flora may reduce enterohepatic recycling of estrogen, thereby potentially diminishing effectiveness of oral contraceptives. Patients should be warned of the possible interaction between antibiotics and oral contraceptives, along with the potential need for an alternate method of contraception during antibiotic therapy.

Pharmacy Drug

VI. ANDROGENS

The androgens are a group of steroids that have anabolic and/or masculinizing effects in both males and females. *Testosterone* [tess-TOSS-te-rone], the most important androgen in humans, is synthesized by Leydig cells in the testes and, in smaller amounts, by thecal cells in the ovaries, and by the adrenal gland in both sexes. Other androgens secreted by the testes are 5α-dihydrotestosterone (DHT),

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androstenedione, and DHEA in small amounts. In adult males, *testosterone* secretion by Leydig cells is controlled by gonadotropin-releasing hormone from the hypothalamus, which stimulates the anterior pituitary gland to secrete FSH and LH. *Testosterone* or its active metabolite, DHT, inhibits production of these specific trophic hormones through a negative feedback loop and, thus, regulates *testosterone* production (Figure 25.11). The androgens are required for (1) normal maturation in the male, (2) sperm production, (3) increased synthesis of muscle proteins and hemoglobin, and (4) decreased bone resorption. Synthetic modifications of the androgen structure modify solubility and susceptibility to metabolism (thus prolonging the half-life of the hormone) and separate anabolic and androgenic effects.

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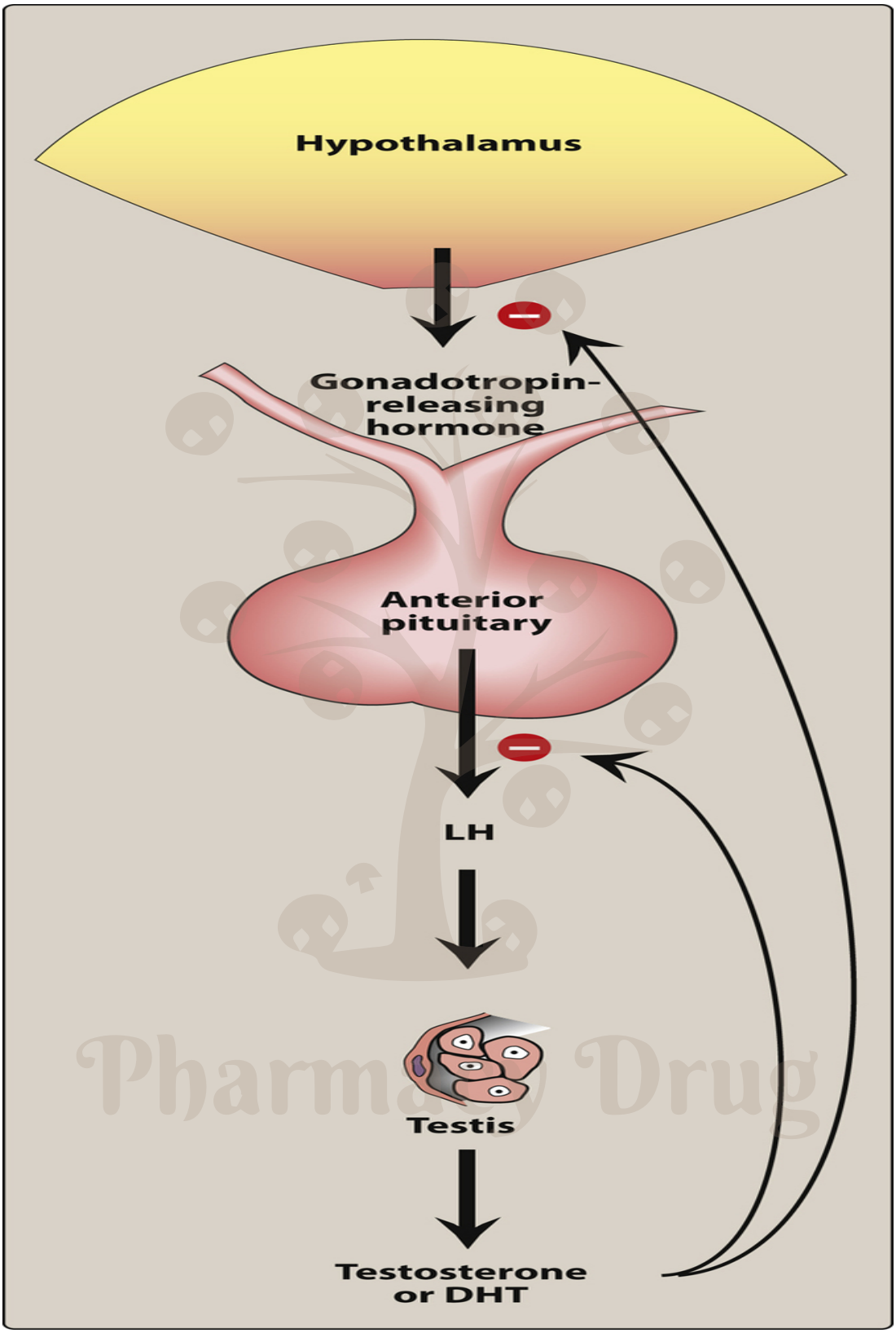

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Figure 25.11 Regulation of secretion of *testosterone*.DHT = 5-α-dihydrotestosterone; LH = luteinizing hormone.

A. Mechanism of action

Like the estrogens and progestins, androgens bind to a specific nuclear receptor in a target cell. Although *testosterone* itself is the active ligand in muscle and liver, in other tissues, it must be metabolized to derivatives, such as DHT. For example, after diffusing into the cells of the prostate, seminal vesicles, epididymis, and skin, *testosterone* is converted by 5α-reductase to DHT, which binds to the receptor.

B. Therapeutic uses

Androgenic steroids (Figure 25.12) are used for males with primary hypogonadism (caused by testicular dysfunction) or secondary hypogonadism (due to failure of the hypothalamus or pituitary). *Testosterone* replacement is primarily indicated for males with hypogonadism related to medical conditions; evidence is lacking for its use in low testosterone associated with aging. *Testosterone* is also used in transgender men to promote virilization in gender affirming hormone therapy. Anabolic steroids can be used to treat chronic wasting associated with human immunodeficiency virus or cancer. An unapproved use of anabolic steroids is to increase lean body mass, muscle strength, and endurance in athletes and body builders (see below). Because of the potential misuse of *testosterone* and its derivatives, these agents are classified as controlled substances. DHEA (a precursor of *testosterone* and estrogen) has been touted as an antiaging hormone as well as a "performance enhancer." There is no definitive evidence that it slows aging, however, or that it improves performance at normal therapeutic doses. Formulations of *testosterone* or its derivatives may be used in combination with estrogen for women with menopausal symptoms unresponsive to estrogen alone. *Danazol* [DAH-nah-zole], a weak androgen, is used in the treatment of endometriosis and fibrocystic breast disease. [Note: *Danazol* also possesses antiestrogenic activity.] Weight gain, acne, decreased breast size, deepening voice, increased libido, and increased hair growth are among the adverse effects.

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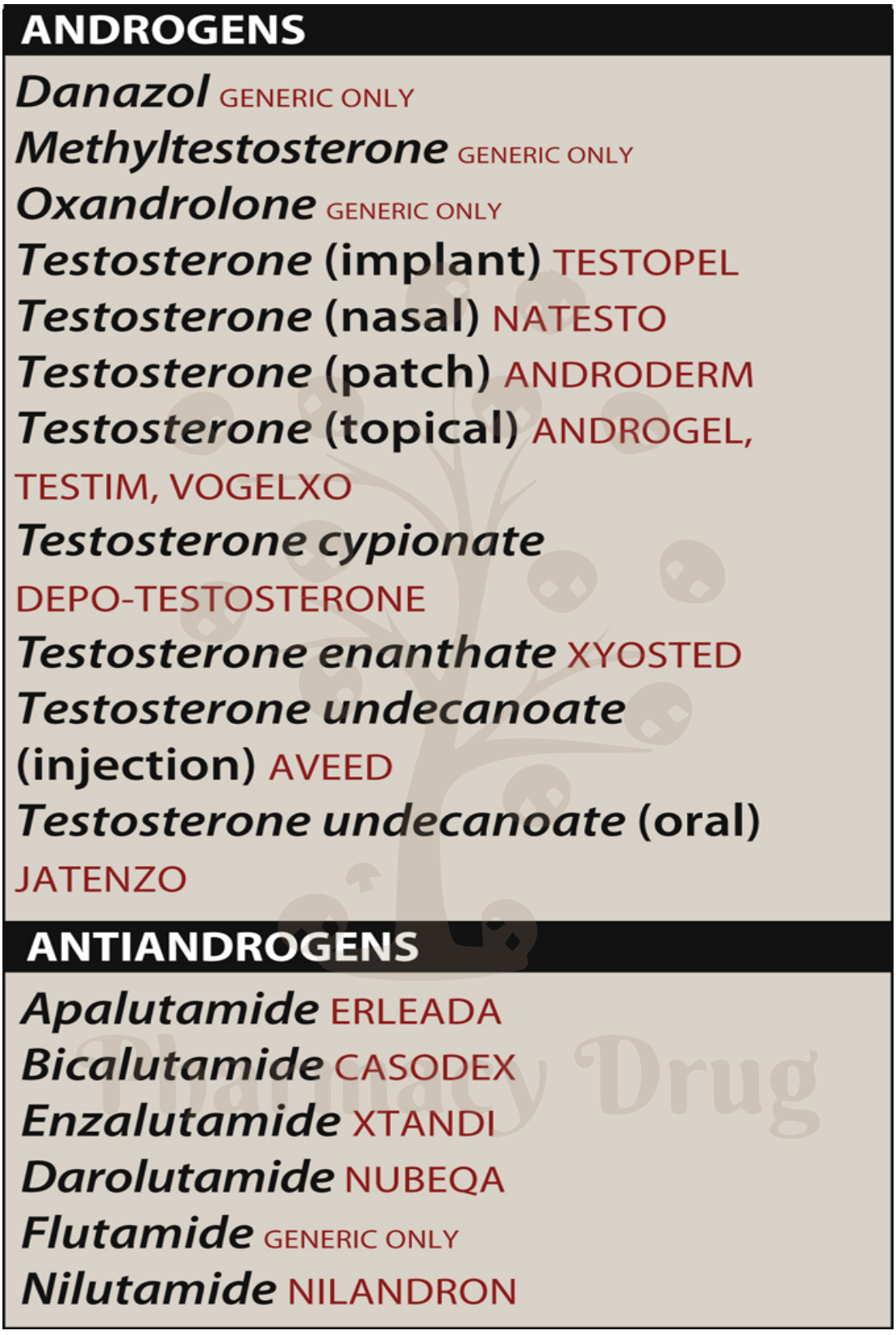

Figure 25.12 Summary of androgens.

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C. Pharmacokinetics

1.Testosterone: This agent is ineffective orally because of inactivation by first-pass metabolism. Therefore, *testosterone* is administered via a transdermal patch, topical gel or solution, nasal gel, or implantable pellet. *Testosterone undecanoate* is an orally active ester prodrug of *testosterone.* This agent may also be administered intramuscularly. Other esters of *testosterone* (for example, *testosterone cypionate* or *enanthate*) are also available for intramuscular administration. The injectable esterified formulations are more lipid soluble and have an increased duration of action up to several weeks. Figure 25.13 shows serum levels of *testosterone* achieved by injection and by a transdermal patch in hypogonadal men. Active metabolites of *testosterone* include DHT and *estradiol*, with activity related to the formation of DHT. Inactive metabolites are excreted primarily in the urine. *Testosterone* and its esters demonstrate a 1:1 relative ratio of androgenic to anabolic activity.

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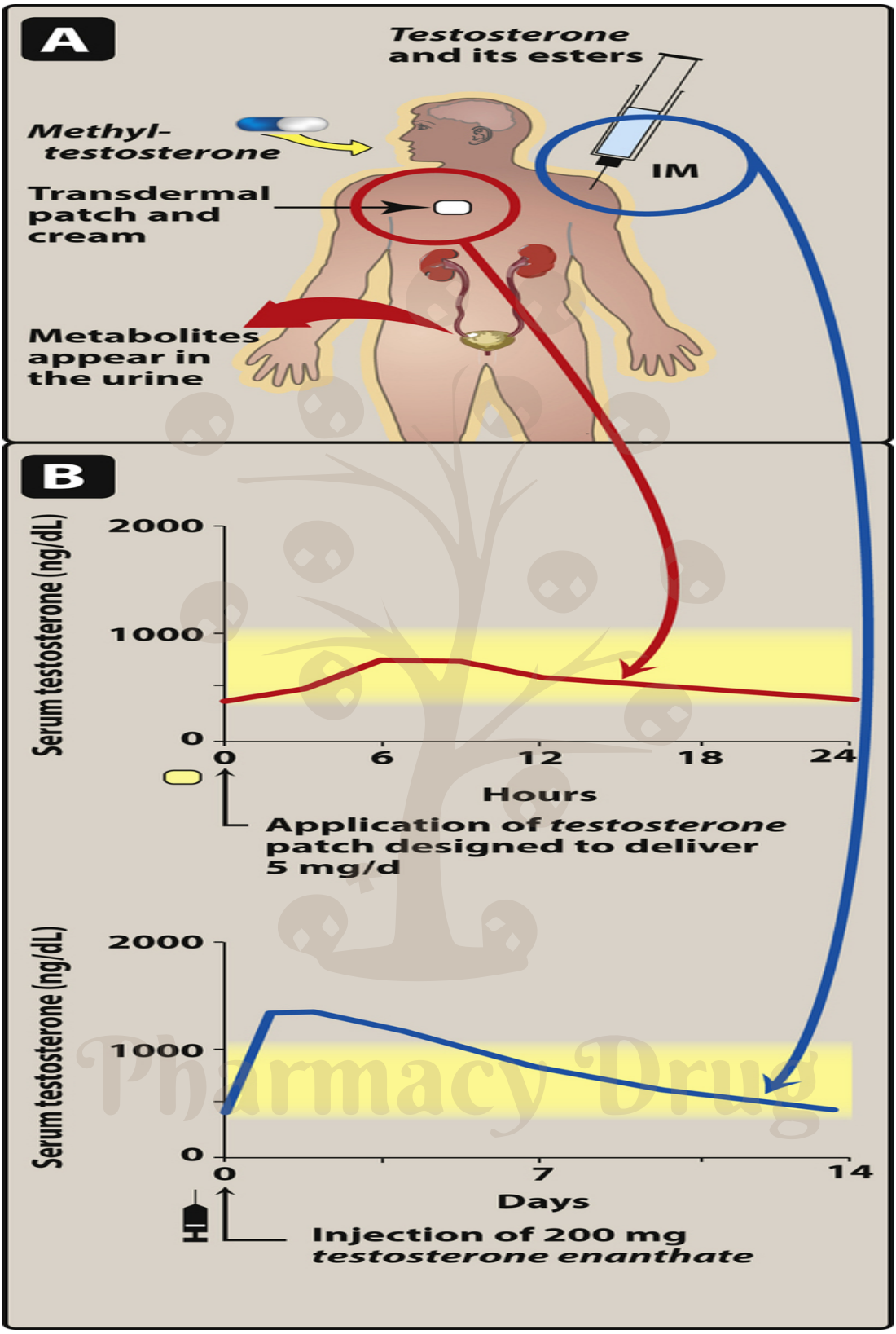

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Figure 25.13 A, Administration and fate of androgens. IM = intramuscular. B, Serum *testosterone* concentrations after administration by injection or transdermal patch to hypogonadal men. The yellow band indicates the upper and lower limits of normal.

2.Testosterone derivatives: Alkylation of the 17α position of *testosterone* is associated with less hepatic metabolism and allows oral administration of the hormone. *Methyltestosterone* is an example of an orally administered *testosterone* derivative. With the availability of increased formulations of *testosterone*, and reports of hepatic dysfunction with this agent, *methyltestosterone* is not recommended for treatment of testosterone deficiency. *Oxandrolone* [ox-AN-droe-lone] is an orally active 17α-alkylated derivative of DHT. *Oxandrolone* has anabolic activity 3 to 13 times that of *testosterone.* This agent is indicated for treatment of cachexia and bone pain associated with osteoporosis.

D. Adverse effects

1.In females: Androgens can cause masculinization, acne, growth of facial hair, deepening of the voice, male pattern baldness, and excessive muscle development. Menstrual irregularities may also occur. *Testosterone* should not be used by pregnant women because of possible virilization of the female fetus.

2.In males: Excess androgen can cause priapism, impotence, decreased spermatogenesis, gynecomastia, and cosmetic changes such as those described for females. Androgens can also increase libido and stimulate growth of the prostate.

3.In children: Androgens can cause abnormal sexual maturation and growth disturbances resulting from premature closing of the epiphyseal plates.

4.General effects: Androgens can increase serum LDL and lower serum high-density lipoprotein levels. They may also cause fluid retention and peripheral edema. *Testosterone* replacement therapy has been associated with a possible increased risk of myocardial infarction and stroke. Hepatic adverse effects have

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been associated with the 17α-alkylated androgens. Local skin irritation is a common adverse effect with topical formulations.

5.In athletes: Use of anabolic steroids (for example, DHEA) by athletes can cause premature closing of the epiphysis of the long bones, which stunts growth and interrupts development. High doses taken by young athletes may result in reduction of testicular size, hepatic abnormalities, increased aggression, major mood disorders, and other adverse effects described above.

E. Antiandrogens

Antiandrogens counter male hormonal action by interfering with the synthesis of androgens or by blocking their receptors. Antiandrogens, such as *flutamide* [FLOO-tah-mide], *bicalutamide* [bye-ka-LOO-ta-mide], *enzalutamide* [enz-a-LOO-ta-mide], and *nilutamide* [nye-LOO-ta-mide], act as competitive inhibitors of androgens at the target cell and are effective orally for the treatment of prostate cancer (see Chapter 37). *Finasteride* [fin-AS-ter-ide] and *dutasteride* [doo-TAS-ter-ride] inhibit 5α-reductase, resulting in decreased formation of dihydrotestosterone. These agents are used for the treatment of benign prostatic hyperplasia (see Chapter 43).

Chapter Summary

- The most common therapeutic uses for estrogens and progestins are contraception and menopausal hormone therapy.
- *Ethinyl estradiol* is the most common estrogen in contraceptive agents. *Estradiol* and *conjugated equine estrogens* are common estrogens in menopausal hormone therapy.
- Hormonal contraceptives may contain a combination of estrogen and progestin (combination oral contraceptives, transdermal patch, or vaginal contraceptive ring) or a progestin-alone (progestin-only pills, injectable, implant, or intrauterine device).
- Estrogen in contraceptives prevents the release of FSH by the pituitary gland, and progestin inhibits LH secretion, thus preventing ovulation. Progestins also thicken cervical mucus.
- LARC methods of contraception (implant and IUD) are the most effective, since efficacy is not reliant on patient adherence.
- Common adverse effects of combined hormonal contraception include breast tenderness, headache, nausea, and changes in mood or libido. Increased blood pressure, hirsutism, and acne may also occur.

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- Estrogen increases the risk of venous thromboembolism, myocardial infarction, and stroke. The risk is increased in older women, smokers, and those with other risk factors, such as hypertension.
- For hormone therapy, the lowest dose of estrogen that controls vasomotor symptoms should be used. Women with an intact uterus must also take a progestin to reduce the risk of endometrial cancer associated with unopposed estrogen.
- Selective estrogen receptor modulators (SERMs) are estrogen-related compounds that display selective agonism or antagonism for estrogen receptors depending on the tissue type. The various SERMs have differing therapeutic applications, including treatment and prevention of breast cancer, as well management of infertility and dyspareunia.
- *Testosterone* replacement is indicated for males with hypogonadism related to medical conditions; evidence is lacking for its use in low testosterone associated with aging.
- Adverse effects of *testosterone* therapy may include acne, increased libido, growth of facial hair, and hypercholesterolemia. With excessive doses male pattern baldness, priapism, and impotence may occur.

STUDY QUESTIONS

Choose the ONE best answer.

25.1 Which of the following best describes the mechanism of action of ethinyl estradiol in oral contraceptives?

A. Delays sperm transport
B. Inhibits release of follicle-stimulating hormone
C. Inhibits release of luteinizing hormone
D. Thickens cervical mucus

Correct answer = B. Exogenously administered estrogen provides negative feedback, which blunts the release of FSH from the pituitary. Progestin inhibits the release of LH, thickens cervical mucus, and, thus, delays sperm transport.

25.2 Which of the following is the most effective form of contraception with typical use?

A. Combined oral contraceptives
B. Progestin-only mini-pill

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C. Depot medroxyprogesterone acetate injection
D. Subdermal progestin implant

Correct answer = D. See Figure 25.9. The subdermal implant is a LARC method of contraception and has a very low failure rate, since it does not require adherence of the patient after implantation. Progestin-only pills are less effective than combined oral contraceptives and the depot medroxyprogesterone acetate injection.

25.3 A 36-year-old woman requests birth control. She has no medical conditions, and she smokes one pack of cigarettes per day. Which of the following would be the most appropriate to recommend?

A. Vaginal contraceptive ring
B. Transdermal contraceptive patch
C. Progestin-only mini-pill
D. Combination oral contraceptive pill

Correct answer = C. Progestin-only products are preferred in older women who are smokers, due to a lower risk of severe adverse effects, such as myocardial infarction and stroke. Estrogen-containing contraceptives are not recommended in women over the age of 35 years who are smokers. The vaginal contraceptive ring, transdermal contraceptive patch, and combination oral contraceptive pills all contain estrogen.

25.4 A 28-year-old breastfeeding mother is 3 weeks postpartum and wants to start hormonal contraception. She plans on trying to have another baby in 1 year. Which is the best contraceptive option for this patient?

A. Ethinyl estradiol and norelgestromin patch
B. Ethinyl estradiol and etonogestrel vaginal ring
C. Norethindrone mini-pill
D. Medroxyprogesterone acetate injection

Correct answer = C. Given the patient is breastfeeding, estrogens should be avoided, as they can decrease milk production, especially in the early postpartum period. Progestins do not decrease milk production. While medroxyprogesterone is a progestin-only contraceptive, it can delay the return of fertility. Fertility returns immediately after discontinuing the use of norethindrone mini-pill, and this agent does not decrease milk supply.

A L G r a w a n y

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25.5 A 25-year-old woman is using injectable medroxyprogesterone acetate as a method of contraception. Which of the following adverse effects is a concern if she wishes to use this therapy long-term?

A. Hyperkalemia
B. Male pattern baldness
C. Osteoporosis
D. Weight loss

Correct answer = C. Medroxyprogesterone acetate may contribute to bone loss and predispose patients to osteoporosis and/or fractures. Therefore, the drug should not be continued long-term unless the patient is not a candidate for other contraceptives. The drug often causes weight gain, not weight loss. The other adverse effects are not associated with medroxyprogesterone.

25.6 A 22-year-old woman requests emergency contraception after unprotected intercourse that occurred 1 day ago. She has no medical conditions. Which of the following agents is most appropriate?

A. Ethinyl estradiol/norgestimate
B. Etonogestrel
C. Levonorgestrel
D. Mifepristone

Correct answer = C. A single dose of levonorgestrel is preferred for emergency contraception and should be administered within 72 hours of unprotected intercourse for best efficacy. Estrogen/progestin regimens are less used for emergency contraception due to a higher incidence of adverse effects such as nausea/vomiting. Etonogestrel is a progestin used in the contraceptive ring and implant. Mifepristone is a progesterone antagonist used to terminate pregnancy.

25.7 A 35-year-old woman is experiencing infertility due to anovulation. Which of the following agents is most appropriate for this patient?

A. Clomiphene
B. Ospemifene
C. Raloxifene

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D. Ulipristal

Correct answer = A. Clomiphene is a SERM that interferes with negative feedback of estrogens on the hypothalamus, thereby increasing the secretion of gonadotropin-releasing hormone and gonadotropins and leading to stimulation of ovulation. Ospemifene is a SERM indicated for the treatment of dyspareunia. Raloxifene is a SERM used in the prevention of breast cancer and osteoporosis. Ulipristal is a progesterone agonist/antagonist used as an emergency contraceptive.

25.8 A 52-year-old woman complains of severe hot flashes that occur several times per day and impact her sleep at night. She had a hysterectomy 7 months ago. Which of the following is the most appropriate therapy for her symptoms?

A. Conjugated equine estrogens (oral)
B. Conjugated equine estrogens with medroxyprogesterone (oral)
C. Estradiol (vaginal cream)
D. Tamoxifen (oral)

Correct answer = A. Systemic administration of estrogens is the most effective therapy for vasomotor symptoms such as hot flashes. Since this patient does not have a uterus (history of hysterectomy), she does not require addition of a progestin such as medroxyprogesterone. Estradiol vaginal cream will provide relief of vaginal dryness and atrophy associated with menopause but will not provide relief of vasomotor symptoms. Tamoxifen is a SERM and may actually worsen hot flashes.

25.9 Which of the following hormonal agents is paired with the most likely adverse effect?

A. Drospirenone–hypokalemia
B. Ethinyl estradiol–hypotension
C. Levonorgestrel–hot flashes
D. Testosterone–increased libido

Correct answer = D. The androgenic effects of testosterone may enhance libido. Drospirenone is an analog of spironolactone and may increase retention of potassium, leading to hyperkalemia. Estrogen in oral contraceptives may increase blood pressure (not reduce blood pressure). The progestin levonorgestrel may have

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androgenic effects (for example, acne and hirsutism). Hot flashes are usually attributed to a lack of estrogen or antagonism of estrogen receptors.

25.10 Use of testosterone is most appropriate in which of the following patients?

A. A 25-year-old competitive athlete
B. A 30-year-old man with hypogonadism due to testicular injury
C. A 50-year-old man with low testosterone related to aging
D. A 65-year-old man with low testosterone and a history of myocardial infarction

Correct answer = B. Testosterone should be used only for hypogonadism associated with documented medical conditions and not low testosterone associated with aging. Testosterone replacement may increase the risk of cardiovascular events and should be used with caution in patients with a history of myocardial infarction and heart disease.

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26

Adrenal Hormones

Shannon A. Miller, Karen L. Whalen

I. OVERVIEW

The adrenal gland consists of the cortex and the medulla. The medulla secretes catecholamines (see Chapter 6), and the cortex secretes two major classes of steroid hormones, the corticosteroids (glucocorticoids and mineralocorticoids; Figure 26.1) and the adrenal androgens. The adrenal cortex has three zones, and each zone synthesizes a different type of steroid hormone from cholesterol (Figure 26.2). The outer zona glomerulosa produces mineralocorticoids (for example, aldosterone) that are responsible for regulating salt and water metabolism. The middle zona fasciculata synthesizes glucocorticoids (for example, cortisol) that are involved with metabolism and response to stress. The inner zona reticularis secretes adrenal androgens (see Chapter 25). Secretion by the two inner zones and, to a lesser extent, the outer zone is controlled by pituitary adrenocorticotropic hormone (ACTH; also called corticotropin), which is released in response to hypothalamic corticotropin-releasing hormone (CRH). Glucocorticoids serve as feedback inhibitors of ACTH and CRH secretion. This chapter provides an overview of corticosteroids, as well as drugs that inhibit production or function of the adrenocorticoids.

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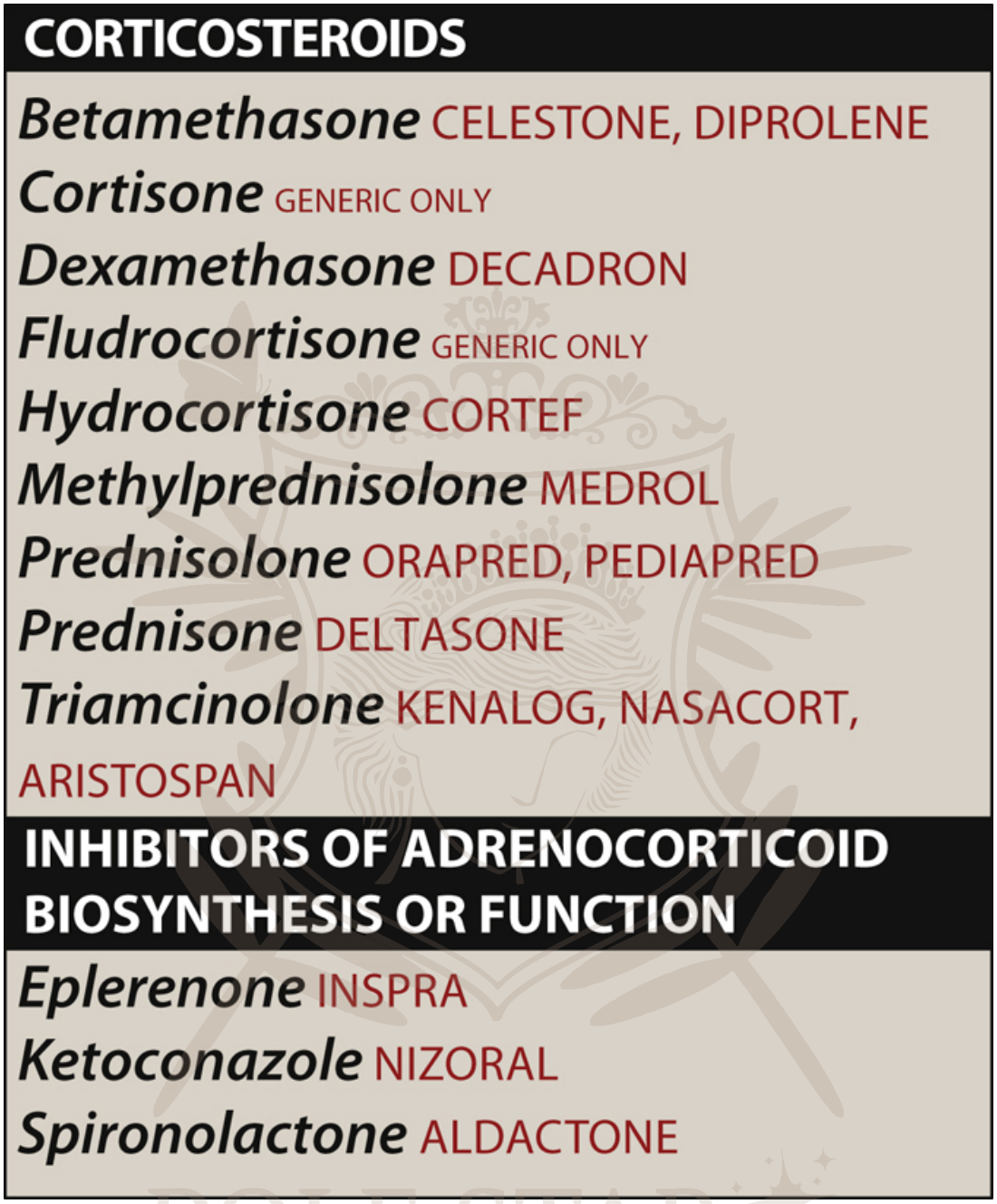

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Figure 26.1 Summary of adrenal corticosteroids.

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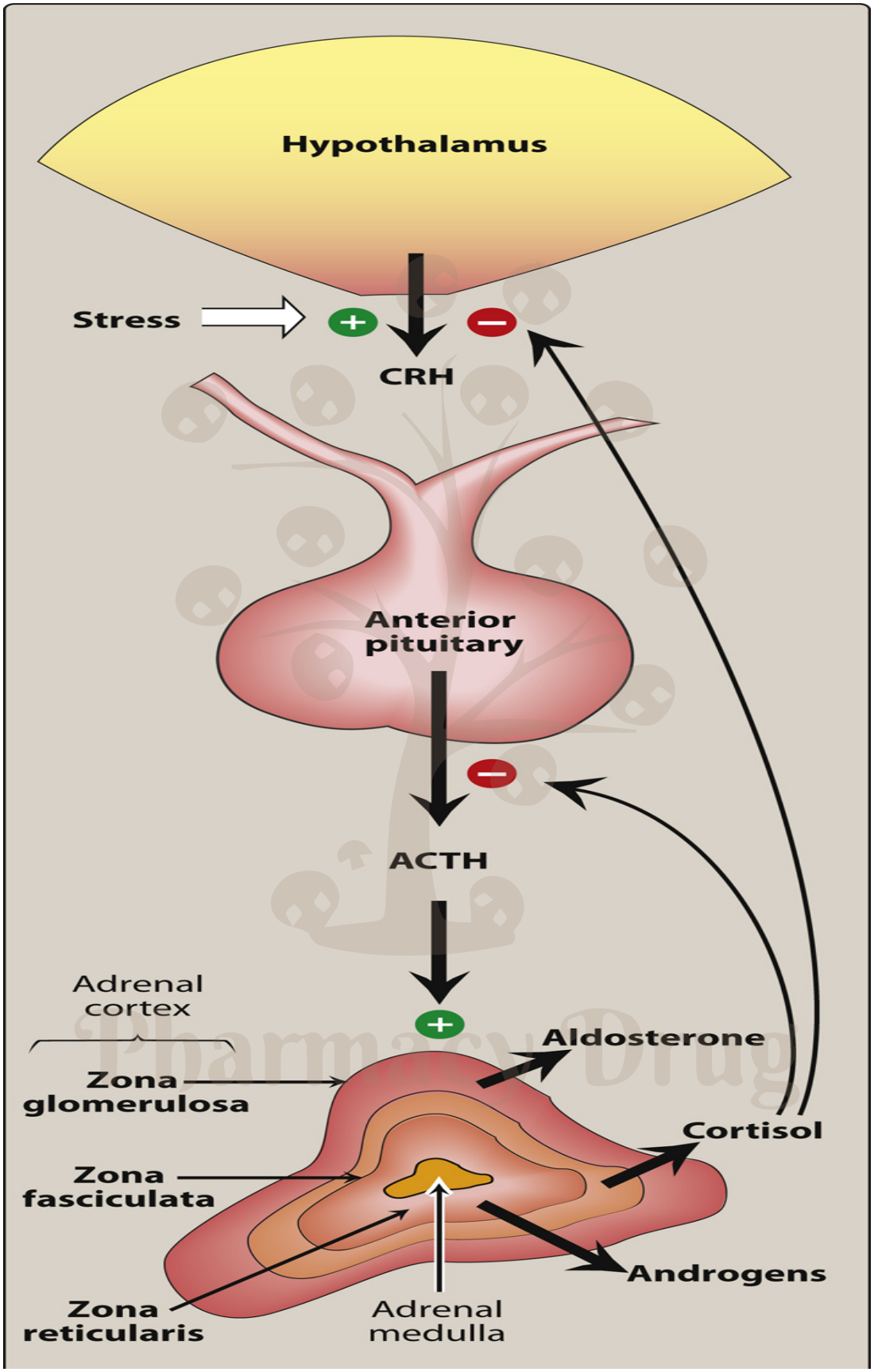

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Figure 26.2 Regulation of corticosteroid secretion.ACTH = adrenocorticotropic hormone; CRH = corticotropin-releasing hormone.

II. CORTICOSTEROIDS

The corticosteroids bind to specific intracellular cytoplasmic receptors in target tissues. Glucocorticoid receptors are widely distributed throughout the body, whereas mineralocorticoid receptors are confined mainly to excretory organs, such as the kidney, colon, salivary glands, and sweat glands. Both types of receptors are found in the brain. After dimerizing, the receptor–hormone complex recruits coactivator (or corepressor) proteins and translocates into the nucleus, where it attaches to gene promoter elements. There it acts as a transcription factor to turn genes on (when complexed with coactivators) or off (when complexed with corepressors), depending on the tissue (Figure 26.3). Because of this mechanism, some effects of corticosteroids take hours to days to occur. This section describes normal actions and therapeutic uses of corticosteroids.

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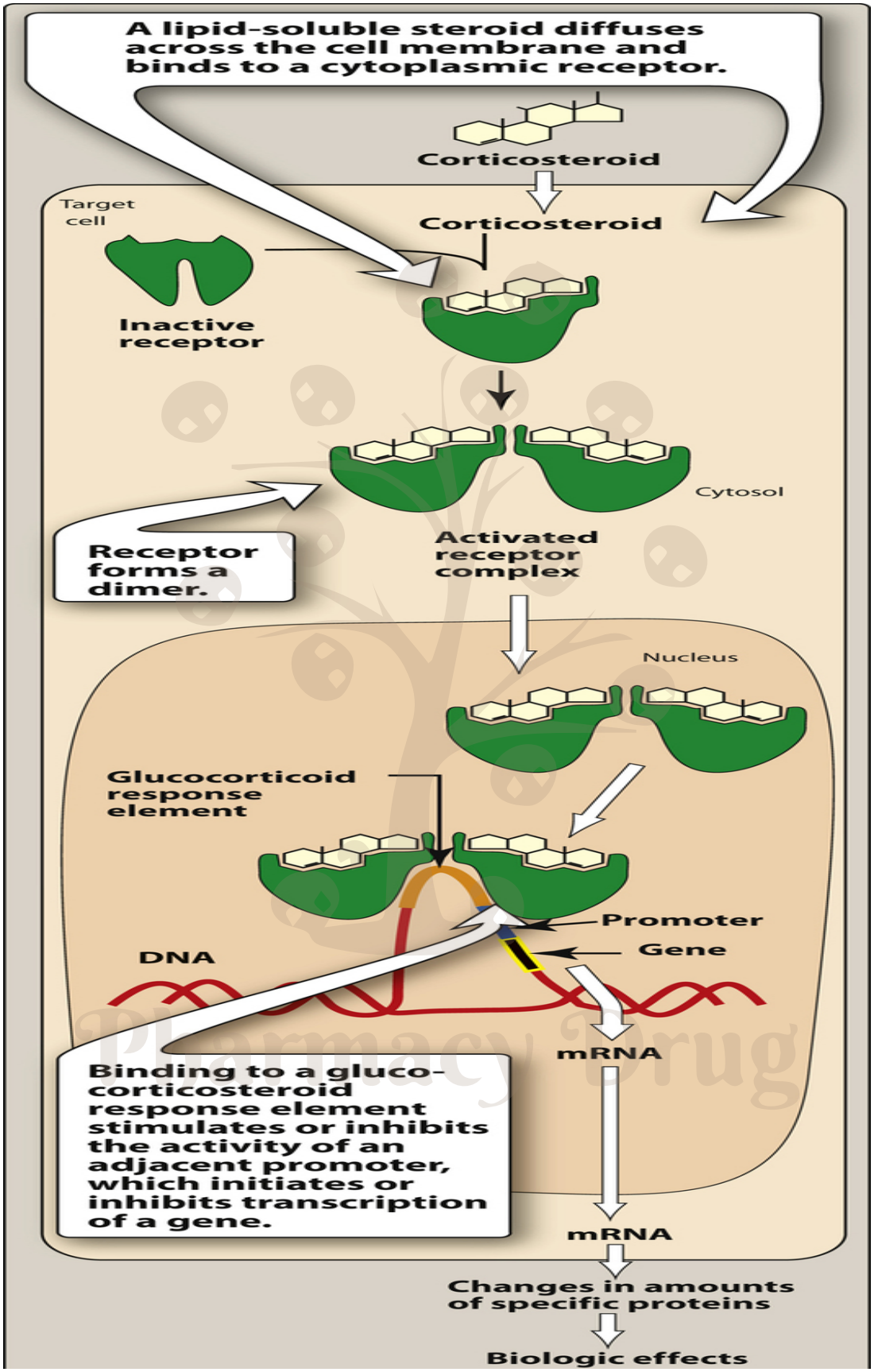

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Figure 26.3 Gene regulation by glucocorticoids.

A. Glucocorticoids

Cortisol is the principal human glucocorticoid. Normally, its production is diurnal, with a peak in early morning followed by a decline and then a secondary, smaller peak in late afternoon. Stress and levels of the circulating steroid influence secretion. The effects of cortisol are many and diverse. In general, all glucocorticoids:

1. **Promote normal intermediary metabolism:** Glucocorticoids stimulate hepatic glucose production by enhancing expression of enzymes involved in gluconeogenesis. They mobilize amino acids and stimulate lipolysis, thereby providing the building blocks and energy for glucose synthesis.

2. **Increase resistance to stress:** By raising plasma glucose levels, glucocorticoids provide the body with energy to combat stress caused by trauma, fright, infection, bleeding, or debilitating disease. [Note: Glucocorticoid insufficiency may result in hypoglycemia (for example, during stressful periods or fasting).]

3. **Alter blood cell levels in plasma:** Glucocorticoids cause a decrease in eosinophils, basophils, monocytes, and lymphocytes by redistributing them from the circulation to lymphoid tissue. Glucocorticoids also increase hemoglobin, erythrocytes, platelets, and polymorphonuclear leukocytes.

4. **Possess anti-inflammatory action:** Potent anti-inflammatory and immunosuppressive activities are the most important therapeutic properties of glucocorticoids. Glucocorticoids lower circulating lymphocytes and inhibit the ability of leukocytes and macrophages to respond to mitogens

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and antigens. Glucocorticoids also decrease the production and release of proinflammatory cytokines. They enhance production of lipocortin, an inhibitor of phospholipase A_2, thereby blocking the release of arachidonic acid (the precursor of the prostaglandins and leukotrienes), and resulting in anti-inflammatory actions. Lastly, these agents influence the inflammatory response by stabilizing mast cell and basophil membranes, thereby decreasing histamine release.

5.Affect other systems: High levels of glucocorticoids provide negative feedback to reduce ACTH production and affect the endocrine system by suppressing synthesis of glucocorticoids and thyroid-stimulating hormone. In addition, adequate cortisol levels are essential for normal glomerular filtration. Corticosteroids may adversely affect other systems (see Adverse Effects below).

B. Mineralocorticoids

Mineralocorticoids help to control fluid status and concentration of electrolytes, especially sodium and potassium. Aldosterone is the primary physiologic mineralocorticoid. Aldosterone acts on mineralocorticoid receptors in the distal tubules and collecting ducts in the kidney, causing reabsorption of sodium, bicarbonate, and water. Conversely, aldosterone decreases reabsorption of potassium, which, with H^+, is lost in the urine. Enhancement of sodium reabsorption by aldosterone also occurs in gastrointestinal mucosa and in sweat and salivary glands. [Note: Elevated aldosterone levels may cause alkalosis and hypokalemia, retention of sodium and water, and increased blood volume and blood pressure. Hyperaldosteronism is treated with *spironolactone*, a potassium-sparing diuretic that also acts as a mineralocorticoid (aldosterone) receptor antagonist.]

C. Therapeutic uses of corticosteroids

Semisynthetic derivatives of corticosteroids vary in anti-inflammatory potency, mineralocorticoid activity, and duration of

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action (Figure 26.4). These agents are used in replacement therapy and in the treatment of severe allergic reactions, asthma, rheumatoid arthritis, other inflammatory disorders, and some cancers.

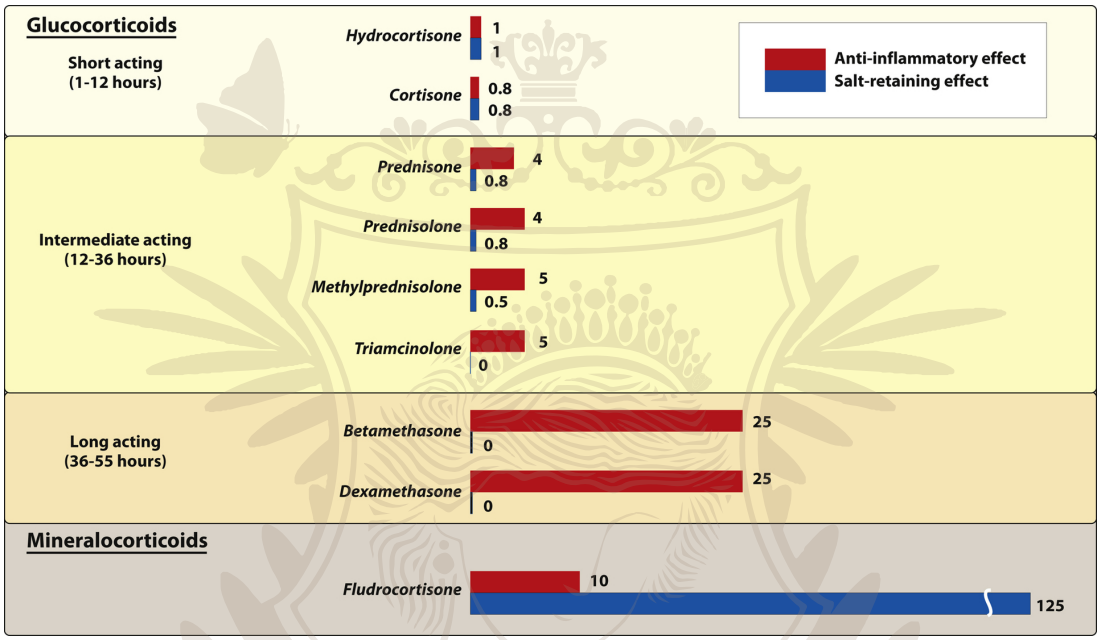

Figure 26.4 Pharmacologic effects and duration of action of some commonly used natural and synthetic corticosteroids.Activities are all relative to that of *hydrocortisone*, which is considered to be 1.

1.Relief of inflammatory symptoms: Corticosteroids significantly reduce inflammation associated with inflammatory skin conditions, including redness, swelling, heat, and tenderness. In addition, these agents are important for symptom control in persistent asthma, as well as in the treatment of exacerbations of asthma, rheumatoid arthritis, inflammatory bowel disease, and other autoimmune disorders. In osteoarthritis, intraarticular corticosteroids may be used for treatment of a disease flare. Corticosteroids are not curative in these disorders.

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2.Treatment of asthma and allergies: Corticosteroids are beneficial in the treatment of allergic rhinitis, as well as drug, serum, and transfusion allergic reactions. In the treatment of allergic rhinitis and asthma, *fluticasone* [floo-TIK-a-sone] and others (see Figure 26.5) are inhaled into the respiratory tract. Inhaled corticosteroids used on a daily basis provide long-term control of the symptoms of asthma and allergic rhinitis (see Chapter 41). Use of inhaled corticosteroids minimizes systemic effects, reducing or eliminating the need for oral corticosteroids.

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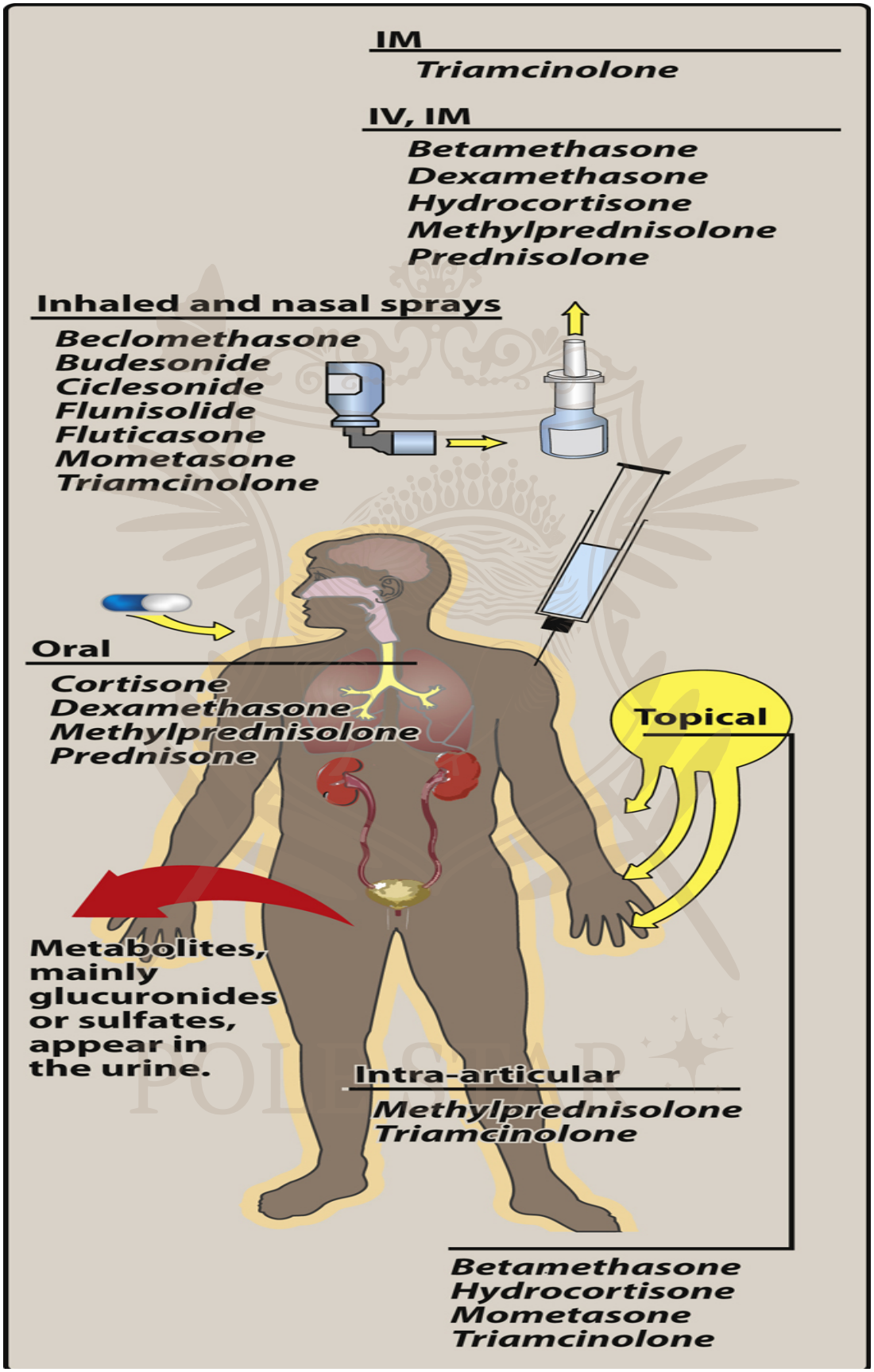
IM
Triamcinolone
IV, IM
Betamethasone
Dexamethasone
Hydrocortisone
Methylprednisolone
Prednisolone
Inhaled and nasal sprays
Beclomethasone
Budesonide
Ciclesonide
Flunisolide
Fluticasone
Mometasone
Triamcinolone
Oral
Cortisone
Dexamethasone
Methylprednisolone
Prednisone
Topical
Metabolites, mainly glucuronides or sulfates, appear in the urine.
Intra-articular
Methylprednisolone
Triamcinolone
Betamethasone
Hydrocortisone
Mometasone
Triamcinolone

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Figure 26.5 Routes of administration and elimination of corticosteroids.IM = intramuscular; IV = intravenous.

3. **Replacement therapy for primary adrenal insufficiency (addison disease):** Addison disease is caused by dysfunction of the adrenal cortex (diagnosed by lack of response to ACTH administration). Patients may present with fatigue, weight loss, hypotension, salt craving, and musculoskeletal or gastrointestinal complaints. In severe cases, patients may experience shock. *Hydrocortisone* [hye-droe-KOR-tih-sone], which is identical to natural cortisol, is given to correct the deficiency. Failure to do so results in death. Two-thirds of the daily dosage of *hydrocortisone* is administered in the morning and one-third in the afternoon, mimicking the normal diurnal variation in cortisol levels. Once-daily *prednisone* [PRED-nih-sone] or *dexamethasone* [dex-a-METH-a-sone] are longer-acting treatment alternatives. Administration of *fludrocortisone* [floo-droe-KOR-tih-sone], a potent synthetic mineralocorticoid, may also be necessary to correct mineralocorticoid deficiency.

4. **Replacement therapy for secondary or tertiary adrenal insufficiency:** Secondary and tertiary adrenal insufficiency are caused by a defect in ACTH production by the pituitary or in CRH production by the hypothalamus, respectively. *Hydrocortisone* is used for treatment of these deficiencies.

5. **Diagnosis of cushing syndrome:** Cushing syndrome is caused by hypersecretion of glucocorticoids (hypercortisolism) that results from excessive release of ACTH by the anterior pituitary, an adrenal tumor, or an ectopic ACTH-producing tumor (secretion of ACTH by a nonpituitary tumor). [Note: Chronic treatment with high doses of glucocorticoids is a frequent cause of Cushing syndrome.] Cortisol levels (urine,

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plasma, and saliva) and the *dexamethasone* suppression test are used to diagnose Cushing syndrome. The synthetic glucocorticoid *dexamethasone* suppresses cortisol release in normal individuals but not those with Cushing syndrome.

Clinical Application 26.1: Cushing Syndrome

Cushing syndrome is a condition characterized by cortisol excess (hypercortisolism). It may occur due to excess secretion of ACTH by the pituitary, an adrenal tumor, an ectopic ACTH-producing tumor (for example, small cell lung cancer), or exogenous administration of glucocorticoid medications (iatrogenic Cushing syndrome). [Note: Cushing syndrome caused by excess secretion of ACTH from the pituitary is known as Cushing disease.] Patients with Cushing syndrome may present with central obesity, a round face (sometimes called moon facies), and a fat pad at the back of the neck (buffalo hump). They may also have elevated blood pressure and glucose intolerance.

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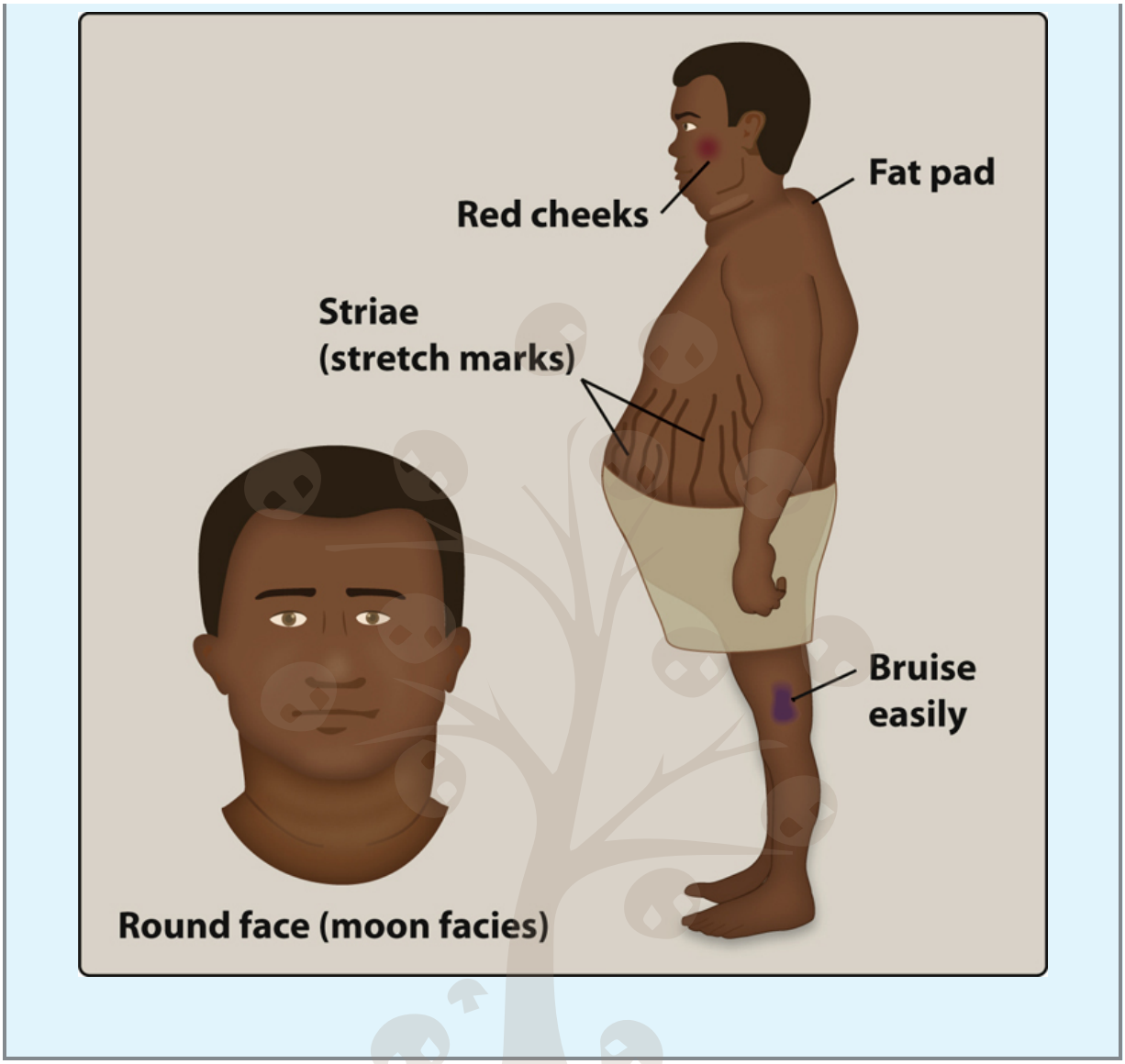

Diagnosis of Cushing syndrome is established with a late-night salivary cortisol level, measurement of 24-hour urine free cortisol, or the *dexamethasone* suppression test. Under normal conditions cortisol is secreted intermittently, with peak levels in the early morning around 7 to 8 am and a nadir late in the evening around midnight. Patients with Cushing syndrome do not have the typical evening nadir in cortisol and demonstrate elevated salivary cortisol levels. With the *dexamethasone* suppression test (DST), a low dose of *dexamethasone* is administered as a single dose in the late evening (or as a series of eight doses over 2 days), and a

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serum cortisol level is drawn at 8 am the following morning. In patients without Cushing syndrome, administration of *dexamethasone* suppresses CRH and ACTH secretion from the hypothalamus and pituitary, respectively, resulting in a low serum cortisol level. In patients with Cushing syndrome, the morning cortisol level is not suppressed. The DST should not be used as a single diagnostic test for Cushing syndrome. Patients who are suspected to have Cushing syndrome based on the results of the DST should have a confirmatory test using one of the other testing methods. [Note: The low-dose DST is used to help diagnose patients who have Cushing syndrome. Once the diagnosis of Cushing syndrome is confirmed, a high-dose DST can be used to differentiate Cushing disease from other forms of Cushing syndrome (adrenal tumor, ectopic ACTH-secreting tumor).] In most cases, treatment of Cushing syndrome involves surgery to resect the pituitary, adrenal glands, or the ectopic ACTH-producing tumor. In cases of iatrogenic Cushing syndrome, the dose of glucocorticoid should be reduced and tapered or alternative medications should be used to manage the disorder that is being treated with glucocorticoids.

6.Replacement therapy for congenital adrenal hyperplasia: Congenital adrenal hyperplasia (CAH) is a group of diseases resulting from an enzyme defect in the synthesis of one or more of the adrenal steroid hormones. CAH may lead to virilization in females due to overproduction of adrenal androgens. Treatment requires administration of sufficient corticosteroids to suppress release of CRH and ACTH and normalize hormone levels. This decreases production of adrenal androgens. The choice of replacement hormone depends on the specific enzyme defect.

7.Acceleration of lung maturation: Respiratory distress syndrome, which is primarily caused by a deficiency of pulmonary surfactant, is seen in premature infants due to their immature lungs. Fetal cortisol is a regulator of lung maturation.

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Consequently, a regimen of *betamethasone* or *dexamethasone* administered intramuscularly to a mother at risk for preterm delivery can accelerate lung maturation in the fetus and prevent respiratory distress syndrome. Ideally the regimen should be initiated at least 48 hours prior to delivery.

D. Pharmacokinetics

1. Absorption and fate: Corticosteroids are readily absorbed after oral administration. Selected compounds may be administered intravenously, intramuscularly, intraarticularly, topically, or via inhalation or intranasal delivery (Figure 26.5). All topical and inhaled glucocorticoids are absorbed to some extent and, therefore, have the potential to suppress the hypothalamic–pituitary–adrenal (HPA) axis. After absorption, glucocorticoids are greater than 90% bound to plasma proteins, mostly corticosteroid-binding globulin or albumin. Corticosteroids are metabolized by the liver microsomal oxidizing enzymes. The metabolites are conjugated to glucuronic acid or sulfate and excreted by the kidney. [Note: The half-life of corticosteroids may increase substantially in hepatic dysfunction.] *Prednisone* is preferred in pregnancy because it minimizes steroid effects on the fetus. It is a prodrug that is not converted to the active compound, *prednisolone* [pred-NIH-so-lone], in the fetal liver. Any *prednisolone* formed in the mother is biotransformed to *prednisone* by placental enzymes.

2. Dosage: Factors that should be considered in determining the dosage of corticosteroids include glucocorticoid versus mineralocorticoid activity, duration of action, type of preparation, and time of day when the drug is administered. When large doses of corticosteroids are required for more than 2 weeks, suppression of the HPA axis occurs. Alternate-day administration of corticosteroids may prevent this adverse effect by allowing the HPA axis to recover/function on days the hormone is not administered.

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E. Adverse effects

Common adverse effects of long-term corticosteroid therapy are often dose related (Figure 26.6). For example, in rheumatoid arthritis, the daily dose of *prednisone* was the strongest predictor of occurrence of adverse effects (Figure 26.7). Osteoporosis is the most common adverse effect with long-term therapy, due to the ability of glucocorticoids to suppress intestinal Ca^{2+} absorption, inhibit bone formation, and decrease sex hormone synthesis. Patients are advised to take calcium and vitamin D supplements. Bisphosphonates may also be useful in the treatment of glucocorticoid-induced osteoporosis. [Note: Increased appetite is not necessarily an adverse effect. In fact, it is one of the reasons for the use of *prednisone* in cancer chemotherapy.] The classic Cushing-like syndrome (redistribution of body fat, puffy face, hirsutism, and increased appetite) is observed in excess corticosteroid replacement. Cataracts may also occur with long-term corticosteroid therapy. Hyperglycemia may develop and lead to diabetes mellitus. Patients with diabetes should monitor blood glucose and adjust medications accordingly when taking corticosteroids. Topical therapy can cause skin atrophy, ecchymosis, and purple striae (see Chapter 45). Inhaled therapy is associated with oral candidiasis, hoarseness, and throat irritation (see Chapter 41).

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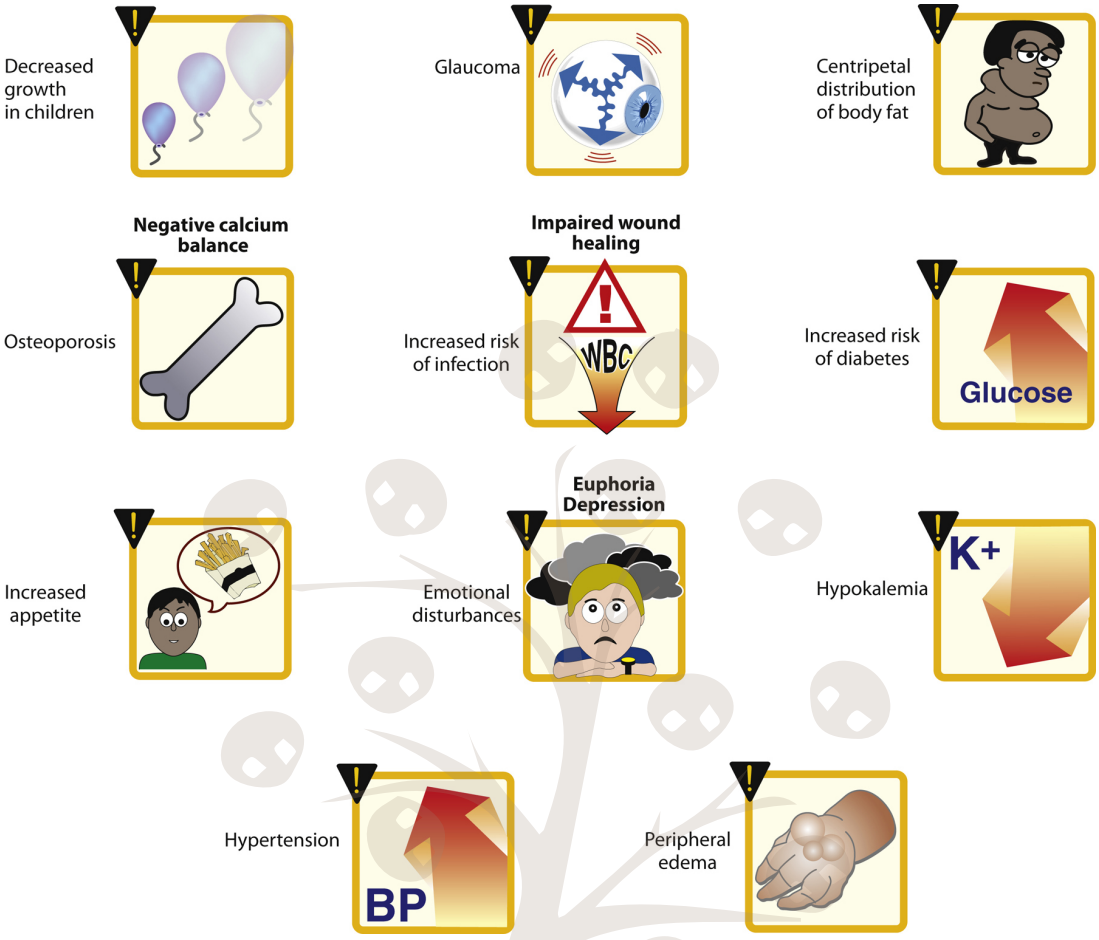

Figure 26.6 Some commonly observed effects of long-term corticosteroid therapy.BP = blood pressure.

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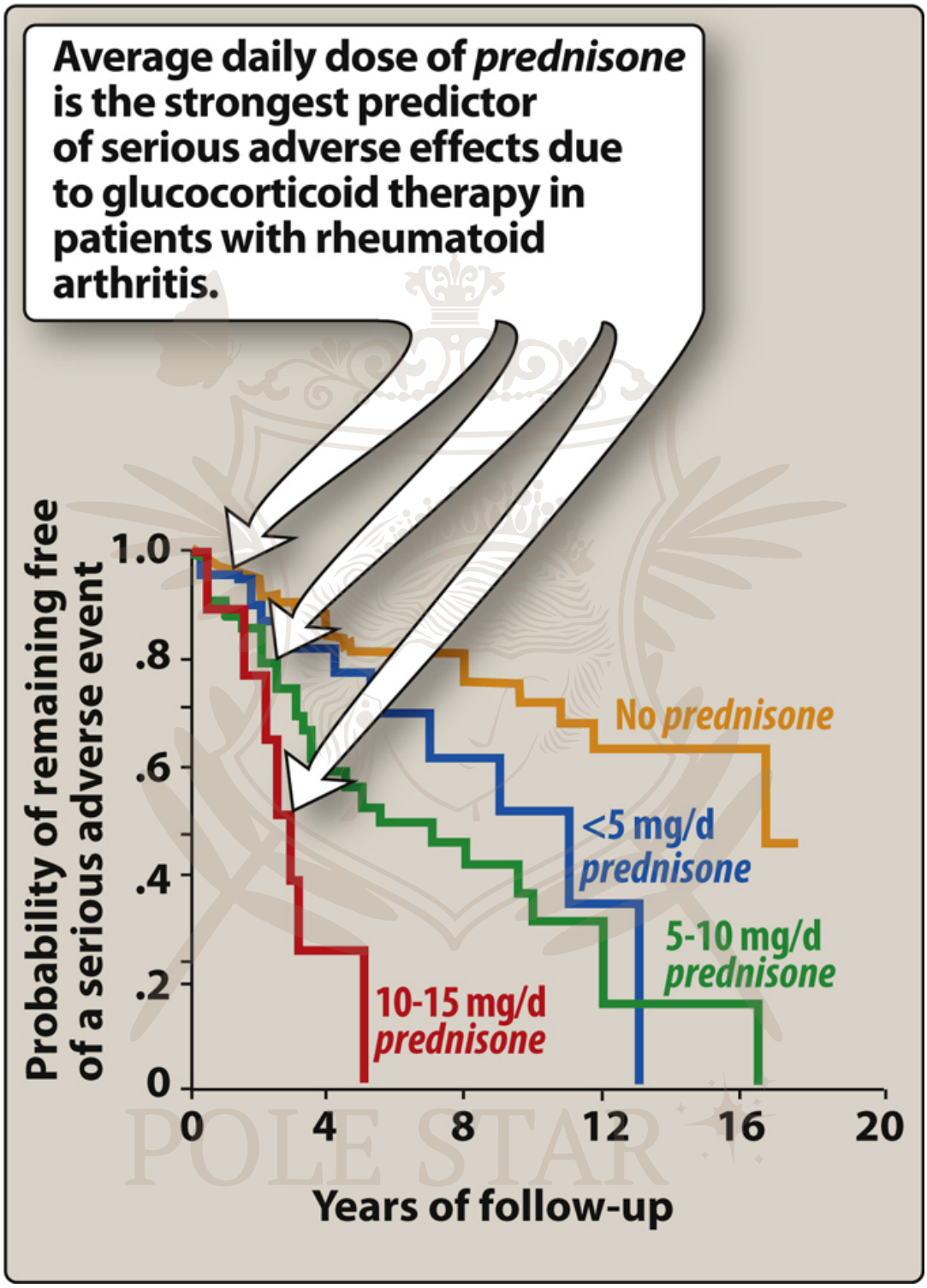

Figure 26.7 Probability of remaining free of a serious adverse event in patients with rheumatoid arthritis treated with no or different doses of *prednisone*.Data from K. G.Saag , R.Koehnke , and J. R.Caldwell , et al.

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Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. *Am. J. Med*. 96: 115 (1994).

F. Discontinuation

Sudden discontinuation of these drugs can cause serious consequences if the patient has suppression of the HPA axis. In this case, abrupt removal of corticosteroids causes acute adrenal insufficiency (adrenal crisis) that can be fatal. Adrenal crisis may manifest with nausea, vomiting, fever, dehydration, hypotension, and, in some cases, shock. Hypoglycemia and hyperkalemia may also occur. The risk of adrenal insufficiency, coupled with the possibility that withdrawal of the corticosteroid could exacerbate the disease being treated with this agent, means that the dose must be tapered slowly according to individual tolerance. The patient must be monitored carefully.

G. Inhibitors of adrenocorticoid biosynthesis or function

Several substances are therapeutically useful as inhibitors of the synthesis or function of adrenal steroids: *ketoconazole*, *spironolactone*, and *eplerenone*.

1. **Ketoconazole:** *Ketoconazole* [kee-toe-KON-ah-zole] is an antifungal agent that strongly inhibits all gonadal and adrenal steroid hormone synthesis. It is used in the treatment of patients with Cushing syndrome when surgical management is not an option.

2. **Spironolactone:** This antihypertensive drug competes for the mineralocorticoid receptor and, thus, inhibits sodium reabsorption in the kidney. *Spironolactone* [speer-oh-no-LAK-tone] also antagonizes aldosterone and testosterone synthesis. *Spironolactone* is effective for the management of hyperaldosteronism, resistant hypertension, and hepatic cirrhosis. It can be used with other standard therapies for treatment of heart failure with reduced ejection fraction (see

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Chapter 10). It is also useful in the management of hirsutism in women, probably due to antiandrogen activity on the hair follicle. Adverse effects include hyperkalemia, gynecomastia, menstrual irregularities, and skin rashes.

3. Eplerenone: *Eplerenone* [e-PLER-ih-none] specifically binds to the mineralocorticoid receptor, where it acts as a selective aldosterone antagonist. The drug has a much lower affinity for the androgen receptor, and this lessens the potential for gynecomastia and irregular menstrual bleeding associated with *spironolactone. Eplerenone* is approved for the treatment of hypertension and for heart failure with reduced ejection fraction after an acute myocardial infarction.

Chapter Summary

- The cortex of the adrenal gland secretes two major classes of steroid hormones, the corticosteroids (glucocorticoids and mineralocorticoids) and the adrenal androgens.
- The outer zona glomerulosa produces mineralocorticoids (for example, aldosterone) that are responsible for regulating salt and water metabolism. The middle zona fasciculata synthesizes glucocorticoids (for example, cortisol) that are involved with metabolism and response to stress. The inner zona reticularis secretes adrenal androgens (see Chapter 25).
- Corticosteroids differ in their metabolic (glucocorticoid) and electrolyte-regulating (mineralocorticoid) activity.
- Cortisol is the principal human glucocorticoid. Potent anti-inflammatory and immunosuppressive activities are the most important therapeutic properties of glucocorticoids.
- Corticosteroids significantly reduce inflammation associated with inflammatory skin conditions. In addition, these agents are important for symptom control in persistent asthma and allergic rhinitis, as well as in the treatment of exacerbations of asthma, rheumatoid arthritis, inflammatory bowel disease, and other autoimmune disorders.
- *Prednisone*, *dexamethasone*, and *methylprednisolone* are examples of commonly used systemic corticosteroids.
- Adverse effects of corticosteroids include mood changes, increased appetite, peripheral edema, hyperglycemia, and increased risk of infection (reduced immunity) and osteoporosis.

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- Cushing-like syndrome (redistribution of body fat, “buffalo hump,” moon facies, striae, and increased appetite) can occur with excess corticosteroid replacement.
- Aldosterone is the primary physiologic mineralocorticoid.
- *Spironolactone* and *eplerenone* are antagonists of aldosterone at the mineralocorticoid receptor. Both agents are useful in selected patients with heart failure with reduced ejection fraction. *Spironolactone* also finds use in hyperaldosteronism, resistant hypertension, hepatic cirrhosis, and management of hirsutism in women.

STUDY QUESTIONS

Choose the ONE best answer.

26.1 Which part of the adrenal gland is correctly paired with the type of substance it secretes?

A. Adrenal medulla—corticotropin
B. Zona fasciculata—cortisol
C. Zona glomerulosa—androgens
D. Zona reticularis—catecholamines

Correct answer = B. The adrenal medulla secretes catecholamines. Corticotropin is secreted by the anterior pituitary. The zona glomerulosa secretes aldosterone, and the zona reticularis secretes androgens.

26.2 Corticosteroids are useful in the treatment of which of the following disorders?

A. Cushing syndrome
B. Diabetes
C. Hypertension
D. Inflammatory bowel disease

Correct answer = D. Corticosteroids can increase blood pressure and glucose and are not used in the treatment of hypertension or diabetes. Cushing syndrome is an excess secretion of glucocorticoids. Dexamethasone may be

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used in the diagnosis of Cushing syndrome but not its treatment. Corticosteroids reduce inflammation and can be used in the management of inflammatory bowel disease.

26.3 Which of the following is a long-acting glucocorticoid?

A. Prednisolone
B. Dexamethasone
C. Hydrocortisone
D. Triamcinolone

Correct answer = B. Dexamethasone is a long-acting agent. Prednisolone and triamcinolone are intermediate-acting agents. Hydrocortisone is short acting.

26.4 A 35-year-old man is prescribed a short course of oral prednisone for an exacerbation of asthma. Which of the following adverse effects is most likely in this patient?

A. Mood changes
B. Hyperkalemia
C. Weight loss
D. Osteoarthritis

Correct answer = A. Use of corticosteroids has been associated with mood swings, including feelings of euphoria and depression. Glucocorticoid therapy may cause hypokalemia, not hyperkalemia. Glucocorticoids also cause increased appetite and osteoporosis.

26.5 A young boy is diagnosed with congenital adrenal hyperplasia. Which is the most appropriate for treatment of this patient?

A. Adrenocorticotropic hormone (ACTH)
B. Ketoconazole
C. Prednisone
D. Spironolactone

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Correct answer = C. Congenital adrenal hyperplasia is seen in infancy and childhood. Because cortisol synthesis is decreased, feedback inhibition of adrenocorticotropic hormone (ACTH) formation and release is also decreased, resulting in enhanced ACTH formation. This in turn leads to increased levels of adrenal androgens and/or mineralocorticoids. The treatment is to administer a glucocorticoid, such as hydrocortisone (in infants) or prednisone, which restores the feedback inhibition. The other options are inappropriate.

26.6 A patient with Addison disease treated with hydrocortisone is experiencing dehydration and hyponatremia. Which drug is best to add to the current therapy?

A. Dexamethasone
B. Fludrocortisone
C. Prednisone
D. Triamcinolone

Correct answer = B. To combat dehydration and hyponatremia, a corticosteroid with high mineralocorticoid activity is needed. Fludrocortisone has the greatest mineralocorticoid activity of the agents provided. The other drugs have little or no mineralocorticoid activity.

26.7 Which of the following strategies is effective to minimize development of HPA axis suppression in a patient with rheumatoid arthritis on long-term high-dose corticosteroid therapy?

A. Alternate-day administration
B. Administration via topical or inhalation route when possible
C. Immediate cessation of the corticosteroid
D. Administration of two-thirds of the daily dose in the morning and one-third in the afternoon

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Correct answer = A. Topical or inhaled corticosteroids may minimize HPA axis suppression but are unlikely to be effective in rheumatoid arthritis. Since the patient has been on long-term therapy, a taper would be necessary.

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Administration of two-thirds of the dose in the morning and one-third in the afternoon is a strategy to mimic the normal diurnal variation of cortisol secretion, but it does not prevent suppression of the HPA axis. Alternate-day administration is beneficial.

26.8 A 33-year-old woman is in preterm labor. Which of the following is most appropriate to administer to her to accelerate fetal lung maturation and prevent respiratory distress syndrome in her newborn?

A. Betamethasone
B. Fludrocortisone
C. Hydrocortisone
D. Prednisone

Correct answer = A. A corticosteroid with high glucocorticoid activity is needed to speed fetal lung maturation prior to delivery. Betamethasone has high glucocorticoid activity and is one of the recommended drugs in this context. Dexamethasone is the other. Fludrocortisone mainly has mineralocorticoid activity and is not useful in this situation. Hydrocortisone has much lower glucocorticoid activity. Prednisone has a higher glucocorticoid activity than hydrocortisone, but the fetus is not able to convert it to prednisolone, the active form.

26.9 A patient with resistant hypertension is found to have a high aldosterone level. Which of the following agents would be most appropriate to add to the current antihypertensive regimen for management of the blood pressure?

A. Dexamethasone
B. Fludrocortisone
C. Ketoconazole
D. Spironolactone

Correct answer = D. Spironolactone is an inhibitor of aldosterone synthesis and is useful in cases of resistant hypertension associated with hyperaldosteronism. Dexamethasone is a corticosteroid and may be associated with an increase (not decrease) in blood pressure. Fludrocortisone has potent mineralocorticoid

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activity and increases blood pressure through retention of sodium and water. Ketoconazole is an azole antifungal. Although it can inhibit aldosterone synthesis, it is not indicated for hypertension. Ketoconazole is rarely used as an antifungal (see Chapter 33) due to significant drug interactions and a risk for hepatotoxicity.

26.1 On physical examination, a 34-year-old woman is noted to have central obesity, elevated blood pressure, moon facies, a dorsal fat pad, and striae. The provider believes she may have Cushing syndrome. Administration of which of the following agents would be beneficial in the diagnosis of Cushing syndrome in this patient?

A. Adrenocorticotropic hormone (ACTH)
B. Dexamethasone
C. Ketoconazole
D. Prednisone

Correct answer = B. The dexamethasone suppression test is a screening test to help detect Cushing syndrome. In patients without Cushing syndrome, administration of dexamethasone suppresses CRH and ACTH secretion from the hypothalamus and pituitary, respectively, resulting in a low serum cortisol level. In patients with Cushing syndrome, the morning cortisol level is not suppressed by administration of dexamethasone. Cushing syndrome is caused by an excess of ACTH, so administration of ACTH is not beneficial. Ketoconazole may be used in the treatment (not diagnosis) of patients with Cushing syndrome when surgical management is not an option. Prednisone is not used in the diagnosis of Cushing syndrome.

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27

Drugs Affecting Bone Metabolism

Karen L. Whalen

I. OVERVIEW

Osteoporosis, Paget disease, and osteomalacia are disorders of the bone. Osteoporosis is characterized by progressive loss of bone mass and skeletal fragility. Patients with osteoporosis have an increased risk of fractures, which can cause significant morbidity. Osteoporosis occurs most frequently in postmenopausal women. It can also occur in older men and in patients who take medications that induce bone loss, such as glucocorticoids. Paget disease is a disorder of bone remodeling that results in disorganized bone formation and enlarged or misshapen bones. Unlike osteoporosis, Paget disease is usually limited to one or a few bones. Patients may experience bone pain, bone deformities, or fractures. Osteomalacia is softening of the bones that is most often attributed to vitamin D deficiency. [Note: Osteomalacia in children is referred to as rickets]. Signs and symptoms of osteomalacia may include bone pain, fractures, and leg weakness. Drug therapy for osteoporosis and Paget disease is outlined in Figure 27.1.

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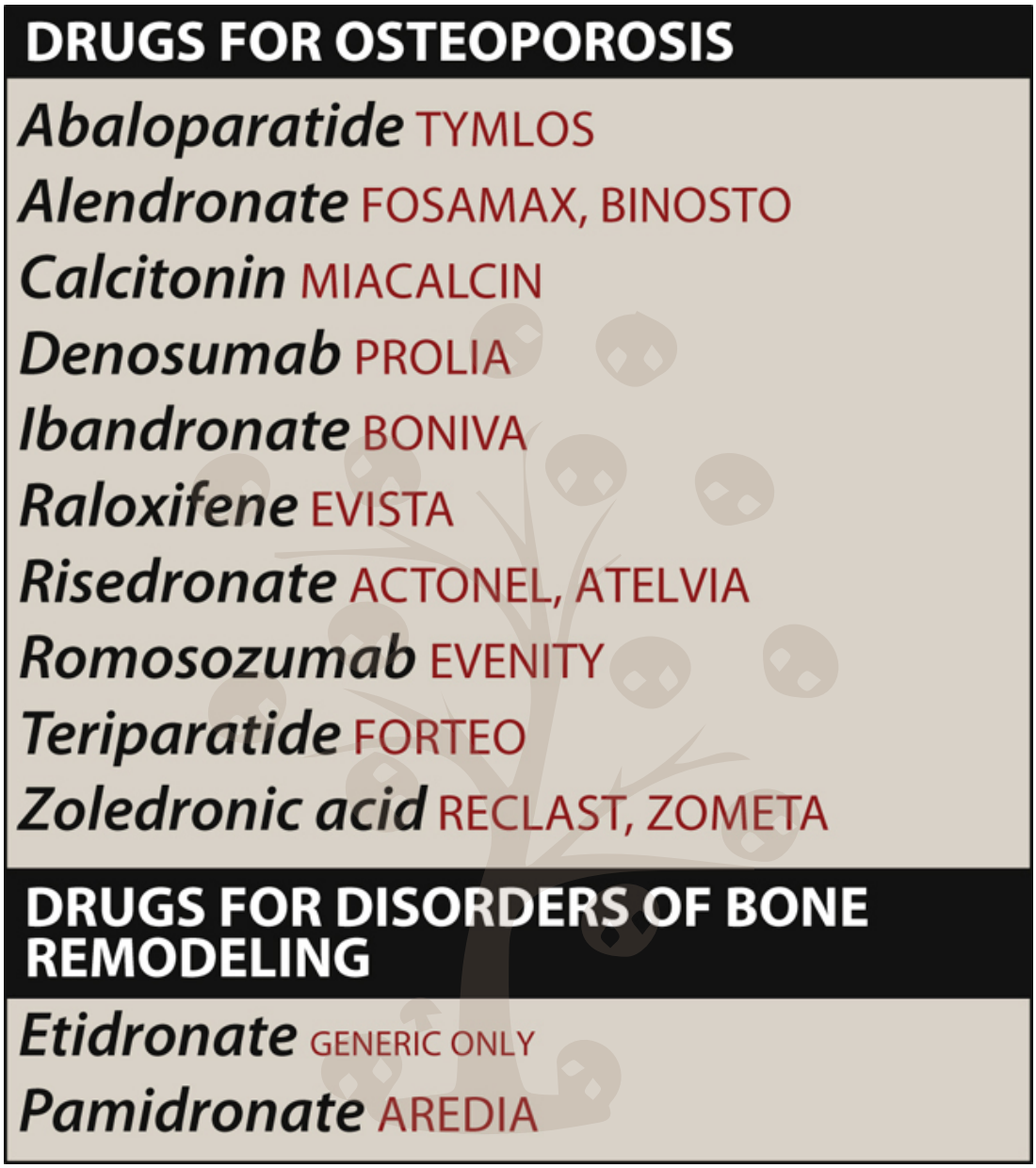

Figure 27.1 Summary of drugs used in the treatment of osteoporosis and other bone disorders.

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II. BONE REMODELING

Throughout life, bone undergoes continuous remodeling, with about 10% of the skeleton replaced each year. Bone remodeling serves to

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remove and replace damaged bone and to maintain calcium homeostasis. Osteoclasts are cells that break down bone, a process known as bone resorption. Following bone resorption, bone-building cells know as osteoblasts synthesize new bone. Crystals of calcium phosphate known as hydroxyapatite are deposited in the new bone matrix during the process of bone mineralization. Bone mineralization is essential for bone strength. Lastly, bone enters a resting phase until remodeling begins again. Bone loss occurs when bone resorption exceeds bone formation during the remodeling process. Figure 27.2 shows changes in bone morphology seen in osteoporosis.

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Figure 27.2 Changes in bone morphology seen in osteoporosis.

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III. PREVENTION OF OSTEOPOROSIS

Strategies to prevent bone loss in postmenopausal women include adequate dietary intake of calcium and vitamin D, weight-bearing exercise, smoking cessation, and avoidance of excessive alcohol intake. Patients with inadequate dietary intake of calcium should receive calcium supplementation. *Calcium carbonate* is an inexpensive and commonly used calcium supplement. It contains 40% elemental calcium and should be taken with meals for best absorption. *Calcium citrate* (21% elemental calcium) is better tolerated and may be taken with or without food. Adverse effects of calcium supplementation include gas, bloating, and constipation. Calcium may interfere with absorption of iron preparations, thyroid replacement, and fluoroquinolone and tetracycline antibiotics; therefore, administration of these drugs should be separated by several hours. *Calcium carbonate* is poorly absorbed with coadministration of histamine-2 receptor antagonists or proton pump inhibitors (see Chapter 42). *Calcium citrate* is preferred in patients taking these acid-reducing agents. Vitamin D is essential for absorption of calcium and bone health, and older patients are often at risk for vitamin D deficiency. Supplementation with vitamin D_2 (*ergocalciferol*) or vitamin D_3 (*cholecalciferol*) is used for treatment. In addition, patients at risk for osteoporosis should avoid drugs that increase bone loss such as glucocorticoids (Figure 27.3), if possible. [Note: Use of glucocorticoids (for example, *prednisone* 5 mg/day or equivalent) for 3 months or more is a significant risk factor for osteoporosis.]

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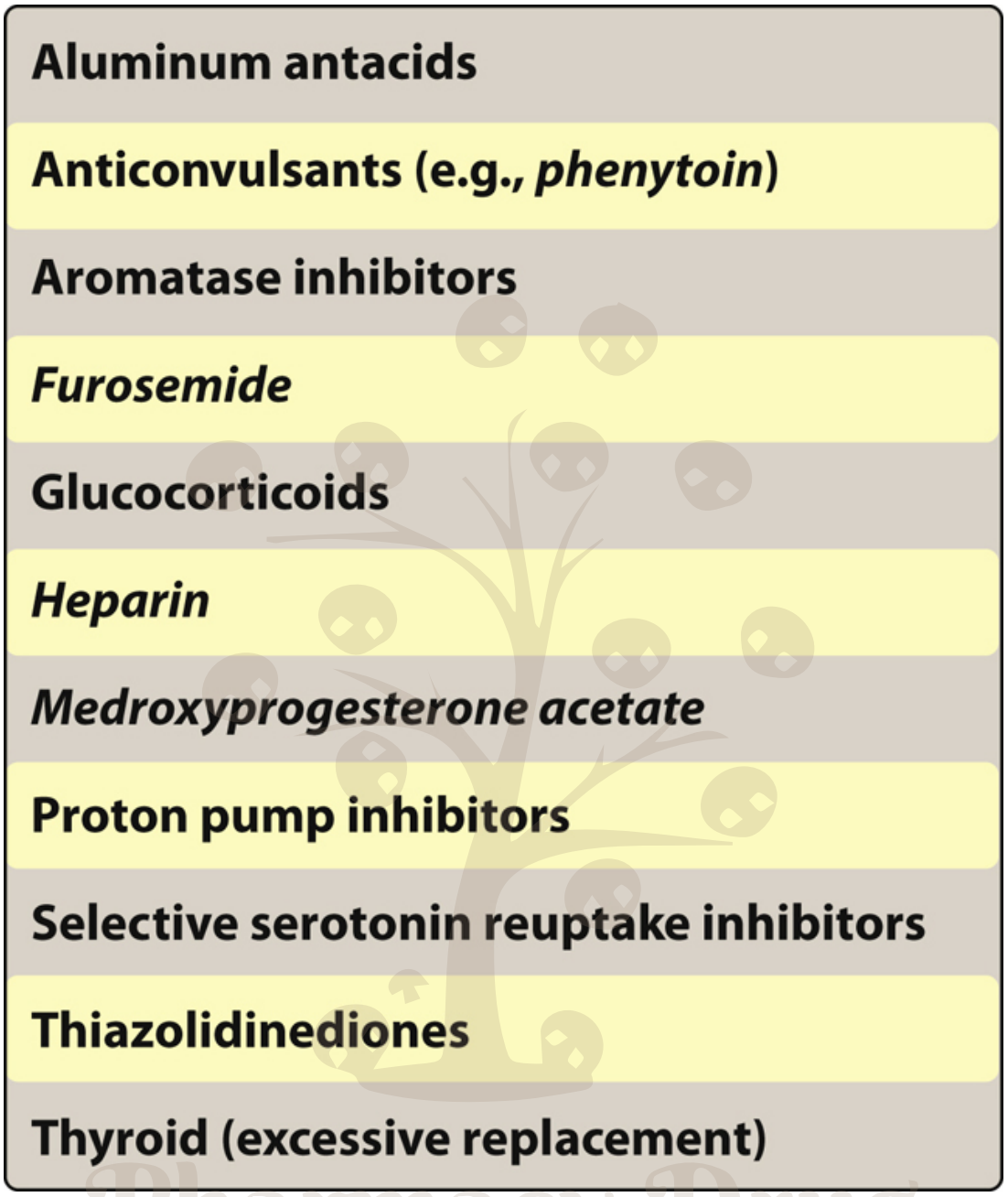

Figure 27.3 Drugs that can contribute to bone loss or increased fracture risk.

IV. TREATMENT OF OSTEOPOROSIS

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Pharmacologic therapy for osteoporosis is warranted in postmenopausal women and men aged 50 years or over who have a previous osteoporotic fracture, a bone mineral density that is 2.5 standard deviations or more below that of a healthy young adult, or a low bone mass (osteopenia) with a high probability of future fractures.

A. Bisphosphonates

Bisphosphonates including *alendronate* [a-LEND-row-nate], *risedronate* [rih-SED-row-nate], and *zoledronic* [zole-DROE-nick] *acid* are preferred agents for the treatment of postmenopausal osteoporosis. These bisphosphonates, along with *etidronate* [e-TID-row-nate], *ibandronate* [eye-BAN-dro-nate], and *pamidronate* [pah-MID-row-nate], comprise an important drug group used for the treatment of bone disorders such as osteoporosis (includes postmenopausal osteoporosis, osteoporosis in men, and glucocorticoid-induced osteoporosis) and Paget disease, as well as for the treatment of bone metastases and hypercalcemia of malignancy.

1. Mechanism of action: Bisphosphonates bind to hydroxyapatite crystals in the bone and decrease osteoclastic bone resorption, resulting in a small increase in bone mass and a decreased risk of fractures in patients with osteoporosis. The beneficial effects of *alendronate* persist over several years of therapy (Figure 27.4), but discontinuation results in a gradual loss of effects. *Zoledronic acid* has a very high affinity for mineralized bone, and it decreases bone resorption for up to 1 year after a single intravenous infusion of the drug. [Note: *Zoledronic acid* is the first-line therapy for the management of Paget disease, due to its high efficacy and once-yearly dosing schedule.] Figure 27.5 shows relative potencies of the bisphosphonates.

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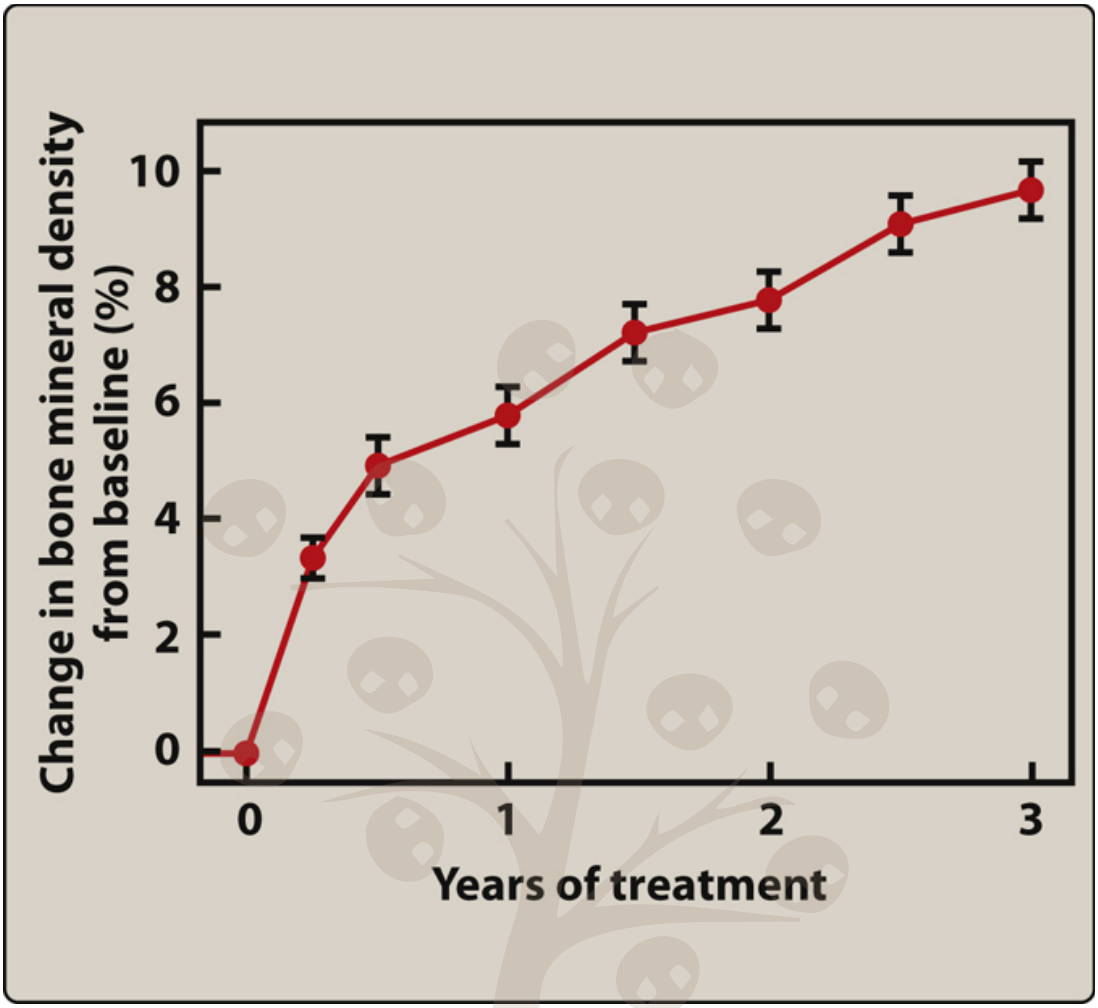

Figure 27.4 Effect of *alendronate* therapy on the bone mineral density of the lumbar spine.

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Bisphosphonate	Antiresorptive activity
Etidronate	1
Tiludronate	10
Pamidronate	100
Alendronate	1000
Risedronate	5000
Ibandronate	10,000
Zoledronic acid	10,000

Figure 27.5 Antiresorptive activity of some bisphosphonates.

2.Pharmacokinetics: The oral bisphosphonates *alendronate*, *risedronate*, and *ibandronate* are dosed on a daily, weekly, or monthly basis depending on the drug (Figure 27.6). Absorption after oral administration is poor, with less than 1% of the dose absorbed. Food and other medications

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significantly interfere with absorption of oral bisphosphonates, and guidelines for administration should be followed to maximize absorption (Figure 27.6). Bisphosphonates are rapidly cleared from the plasma, primarily because they avidly bind to hydroxyapatite in the bone. Once bound to bone, they are cleared over a period of hours to years. Elimination is predominantly via the kidney, and bisphosphonates should be avoided in severe renal impairment. For patients unable to tolerate oral bisphosphonates, intravenous *ibandronate* and *zoledronic acid* are alternatives.

BISPHOSPHONATE	FORMULATION	DOSING FREQUENCY*
Alendronate	Oral tablet Effervescent tablet	Daily or weekly Weekly
Ibandronate	Oral tablet Intravenous	Monthly Every 3 months
Risedronate	Oral tablet Oral delayed-release tablet	Daily, weekly, or monthly Weekly
Zoledronic acid	Intravenous	Yearly

DOSING INSTRUCTIONS FOR ORAL BISPHOSPHONATES

- Take with 6 to 8 ounces of plain water only
  [Note: Take *risedronate* delayed-release tablet with at least 4 ounces of plain water]
- Take at least 30 minutes (60 minutes for *ibandronate*) BEFORE other food, drink, or medications
  [Note: Take *risedronate* delayed-release tablet immediately AFTER breakfast]
- Remain upright and do not lie down or recline for at least 30 minutes (60 minutes for *ibandronate*) after taking

Figure 27.6 Dosage formulations and instructions for administration of bisphosphonates for the treatment of osteoporosis.*Frequency of administration for individual agents varies with dosage, with higher doses administered less frequently.

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3.Adverse effects: Adverse effects include diarrhea, abdominal pain, and musculoskeletal pain. *Alendronate*, *risedronate*, and *ibandronate* are associated with esophagitis and esophageal ulcers. To minimize esophageal irritation, patients should remain upright after taking oral bisphosphonates. Although uncommon, osteonecrosis of the jaw (ONJ) and atypical femur fractures may occur with the use

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of bisphosphonates. Risk factors for ONJ include higher dose and longer duration of therapy, intravenous administration, dental extractions or implants, use of glucocorticoids, diabetes, and smoking. The risk of atypical fractures seems to increase with long-term use of bisphosphonates. Therefore, current guidelines recommend assessment of fracture risk and consideration of a drug holiday (temporary discontinuation of bisphosphonate) for some patients after 5 years of oral bisphosphonates or 3 years of *zoledronic acid.* Bisphosphonate therapy should not be discontinued in women who remain at high risk of fractures.

B. RANKL inhibitor

Denosumab [den-OH-sue-mab] is a monoclonal antibody that targets receptor activator of nuclear factor kappa-B ligand (RANKL). By binding to RANKL, *denosumab* prevents activation of RANK receptors on osteoclasts, thereby inhibiting osteoclast formation and function and reducing bone resorption (Figure 27.7). *Denosumab* is approved for the treatment of postmenopausal osteoporosis in women at high risk of fracture, as well as osteoporosis in men and glucocorticoid-induced osteoporosis. It is administered via subcutaneous injection every 6 months. *Denosumab* is considered an alternative first-line agent for postmenopausal osteoporosis, particularly in patients at higher risk of fractures. The drug has been associated with gastrointestinal upset, bone pain, increased risk of infections, dermatologic reactions, hypocalcemia, and rarely, ONJ, and atypical fractures. If therapy with *denosumab* is discontinued, patients should be started on an alternative agent such as a bisphosphonate to prevent a rebound increase in bone resorption. [Note: A different formulation of *denosumab* has several other indications, including treatment of hypercalcemia of malignancy and prevention of skeletal-related events in patients with multiple myeloma or bone metastases.]

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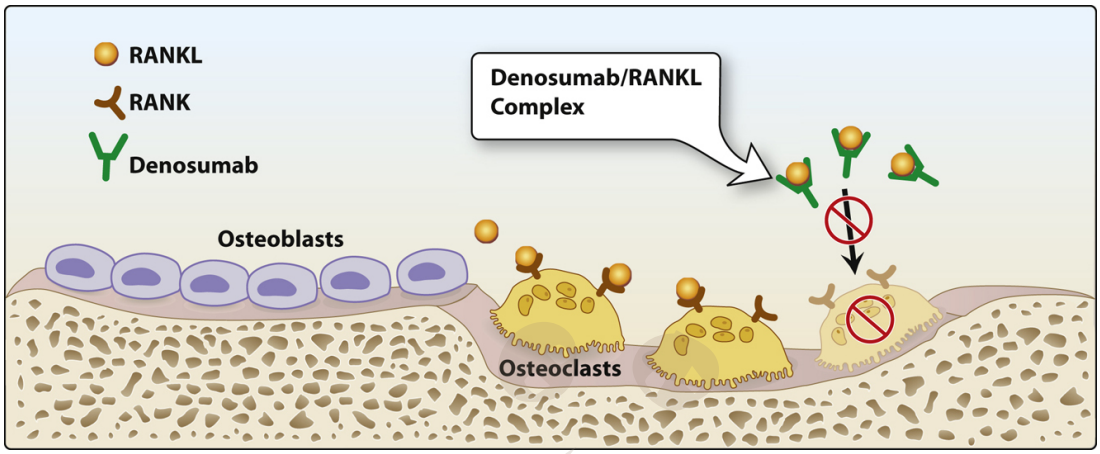

Figure 27.7 Mechanism of action of *denosumab*.RANKL = receptor activator of nuclear factor kappa-B ligand.

C. Parathyroid agents

Teriparatide [ter-ih-PAR-a-tide] is a recombinant form of human parathyroid hormone and *abaloparatide* [a-bal-oh-PAR-a-tide] is an analog of parathyroid hormone–related peptide. These drugs act as agonists at the parathyroid hormone receptor, and once-daily subcutaneous administration results in stimulation of osteoblastic activity and increased bone formation and bone strength. The parathyroid agents should be reserved for patients at high risk of fractures and those who have failed or cannot tolerate other osteoporosis therapies. Adverse effects include injection site reactions, hypercalcemia, and orthostatic hypotension. In addition, hyperuricemia may occur with *abaloparatide.* Both drugs have been associated with an increased risk of osteosarcoma in rats, and these agents are contraindicated in patients at risk for osteosarcoma. Cumulative lifetime use of either agent for more than 2 years is not recommended. Following completion of therapy with *teriparatide* or *abaloparatide*, another antiresorptive agent for osteoporosis should be initiated to maintain bone mineral density and prevent future bone loss.

D. Sclerostin inhibitor

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Romosozumab [ROE-moe-SOZ-ue-mab] is a monoclonal antibody and an inhibitor of sclerostin. Sclerostin is an important regulatory factor in bone remodeling, where it inhibits bone formation. *Romosozumab* binds to sclerostin and inhibits its action, thereby promoting osteoblast activity and bone formation. A secondary and lesser mechanism of action is a decrease in bone resorption. *Romosozumab* is indicated in women with postmenopausal osteoporosis who have a high risk of fractures. It is administered as a once-monthly subcutaneous injection for 12 months. [Note: Two injections are required to administer the full dosage.] Adverse effects include arthralgias, headache, and injection site reactions. The drug should be avoided in patients with a history of myocardial infarction or stroke, as a small but significant increase in these events occurred in clinical trials. After 12 months of therapy with *romosozumab* is completed, therapy with other antiresorptive agents should be initiated.

E. Selective estrogen receptor modulators

Lower estrogen levels after menopause promote proliferation and activation of osteoclasts, and bone mass can decline rapidly. Estrogen replacement is effective for the prevention of postmenopausal bone loss. However, since estrogen may increase the risk of endometrial cancer (when used without a progestin in women with an intact uterus), breast cancer, stroke, venous thromboembolism, and coronary events, it is no longer routinely recommended as a therapy for osteoporosis. [Note: Estrogen therapy for osteoporosis may be considered for women with severe symptoms of menopause and contraindications or intolerance to first-line agents for osteoporosis.] *Raloxifene* [rah-LOX-ih-feen] is a selective estrogen receptor modulator (SERM) approved for the prevention and treatment of osteoporosis in postmenopausal women. It has estrogen-like effects on bone and estrogen antagonist effects on breast and endometrial tissue. Therefore, *raloxifene* increases bone density without increasing the risk of endometrial cancer. It also decreases the risk of invasive breast cancer. Because it has not been shown to reduce

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nonvertebral or hip fractures, *raloxifene* should be used as an alternative treatment for postmenopausal osteoporosis in women who cannot take bisphosphonates or *denosumab.* Adverse effects include hot flashes, leg cramps, and increased risk of venous thromboembolism. *Raloxifene* should be avoided in patients with a history of thromboembolic disease (pulmonary embolism or deep venous thrombosis). [Note: *Bazedoxifene* (not available as a single agent in the United States) is another SERM that may be used for the treatment of postmenopausal osteoporosis.]

F. Calcitonin

Calcitonin, a peptide secreted by the thyroid gland, binds to osteoclasts and inhibits their resorptive activity. Salmon *calcitonin* [cal-SIH-toe-nin] has a greater potency and a longer duration of action than human calcitonin. It is indicated for the treatment of osteoporosis in women who are at least 5 years postmenopausal. The drug reduces bone resorption, but it is less effective than other agents. It is also associated with a higher risk of new malignancy with long-term administration. Therefore, *calcitonin* should only be used for the treatment of osteoporosis if other agents are inappropriate or not tolerated. A unique property of *calcitonin* is relief of pain associated with osteoporotic fracture. Therefore, *calcitonin* is sometimes prescribed for the short-term treatment of patients with a recent painful vertebral fracture. *Calcitonin* is available in an intranasal or injectable formulation (subcutaneous or intramuscular administration). Rhinitis and injection site reactions are the most common adverse effects with the intranasal and injectable formulations, respectively. [Note: *Calcitonin* is used more frequently for the management of hypercalcemia (injectable formulation) than the treatment of osteoporosis.]

Clinical Application 27.1: Diagnosis and Management of Postmenopausal Osteoporosis

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Dual-energy X-ray absorptiometry (DXA) is a diagnostic imaging technique that uses low levels of radiation to assess bone mineral density. Results of the DXA scan are reported as a T-score, which represents the bone mineral density of the patient as compared to young healthy adults. Patients are considered to have osteoporosis if they have a bone mineral density that is 2.5 standard deviations or more below that of a young healthy patient (T-score ≤ –2.5). Patients may also be diagnosed with osteoporosis if they have a fracture of the hip, spine, wrist, or other area that occurs with no or minimal trauma.

Drug therapy for the treatment of osteoporosis should be initiated in patients who meet one of the above criteria (T-score ≤ –2.5 or history of fragility fracture) to prevent future fractures and morbidity associated with osteoporosis. In addition, patients with low bone mass (also called osteopenia; T-score between –1.0 and –2.5) may be candidates for drug therapy depending on the risk of future fractures. Fracture risk can be calculated using a tool such as the Fracture Risk Assessment Tool (FRAX; https://www.sheffield.ac.uk/FRAX/). Current guidelines recommend drug therapy for patients with osteopenia and a 10-year probability of hip fracture of 3% or greater or a 10-year probability of major osteoporosis fracture of 20% or more. [Note: Thresholds for initiation of osteoporosis therapy may vary depending on the country or region of the world.] First-line therapy for osteoporosis includes treatment with bisphosphonates or *denosumab* as an alternative. *Teriparatide*, *abaloparatide*, and *romosozumab* should be reserved for individuals at very high risk of fractures (for example, T-score below –2.5 with fractures, or history of multiple vertebral fractures). After initiation of drug therapy, a DXA scan should be performed every 1 to 3 years to assess effects on bone mineral density.

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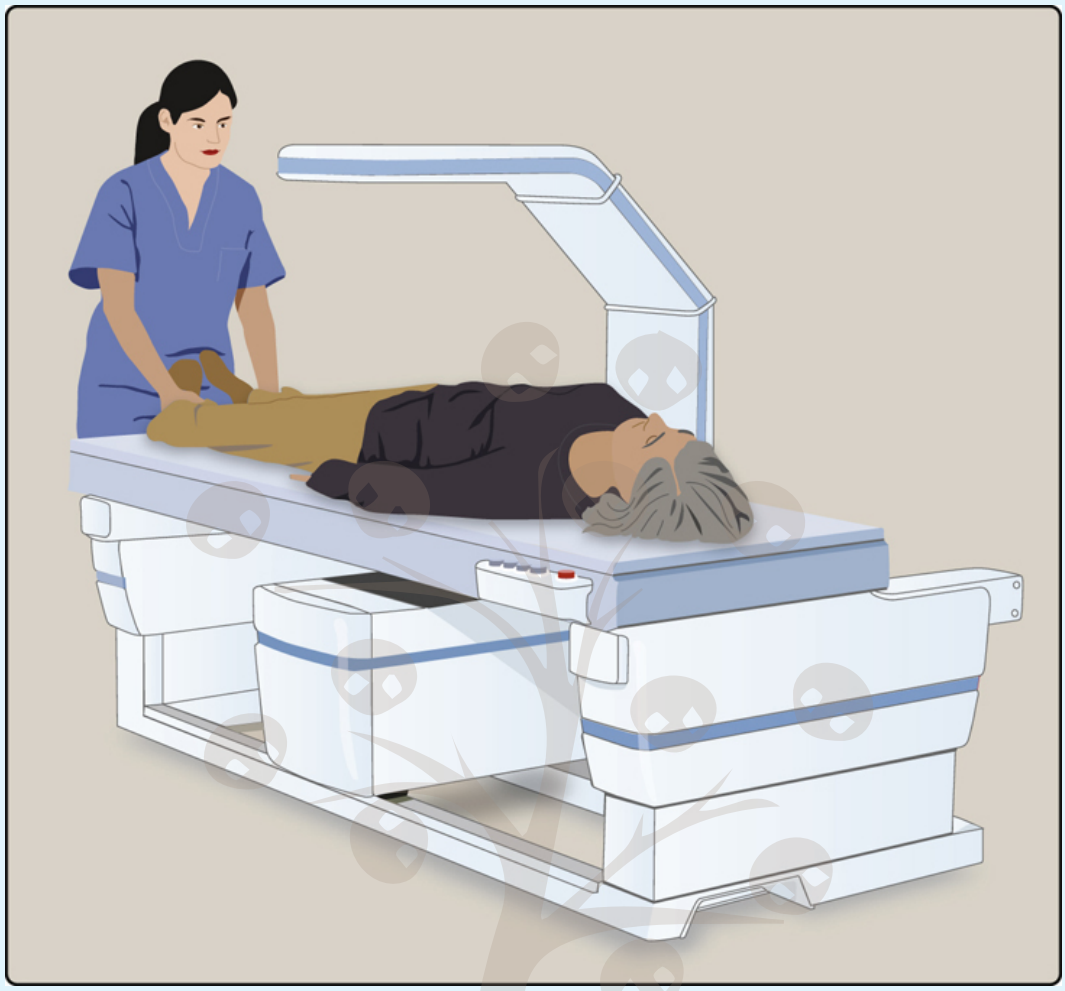

Dual-energy X-ray absorptiometry is used to assess the bone mineral density.

Chapter Summary

- Bisphosphonates including *alendronate*, *risedronate*, and *zoledronic acid* are preferred agents for the treatment of postmenopausal osteoporosis.
- Bisphosphonates bind to hydroxyapatite crystals in the bone and decrease osteoclastic bone resorption, resulting in an increase in bone mass and a decreased risk of fractures. The effects of bisphosphonates on bone are long-lasting.
- Oral bisphosphonates for osteoporosis (*alendronate*, *risedronate*, *ibandronate*) are associated with esophagitis and esophageal ulcers. To minimize esophageal irritation, patients should remain upright after taking oral bisphosphonates.

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- Food and other medications significantly interfere with absorption of oral bisphosphonates.
- Intravenous bisphosphonates for osteoporosis include *zoledronic acid* and *ibandronate. Zoledronic acid* is administered once per year as an intravenous infusion.
- Rare, but serious, adverse effects of the bisphosphonates include ONJ and atypical femur fractures. These effects are more likely with a longer duration of therapy. Therefore, a drug holiday should be considered for patients after 5 years of oral bisphosphonates or 3 years of *zoledronic acid.*
- *Denosumab* is a RANKL inhibitor that is an alternative first-line agent for postmenopausal osteoporosis, particularly in patients at higher risk of fractures. It is administered every 6 months as a subcutaneous injection.
- The parathyroid agents *teriparatide* and *abaloparatide* act as agonists at the parathyroid hormone receptor to stimulate osteoblastic activity and increase bone formation and strength. Due to the risk of osteosarcoma, use of these agents is limited to 2 years.
- *Romosozumab* is a sclerostin inhibitor, thereby promoting osteoblast activity and bone formation. It is administered as a once-monthly subcutaneous injection for 12 months.
- In the treatment of osteoporosis, *teriparatide*, *abaloparatide*, and *romosozumab* should be reserved for individuals at very high risk of fractures.

STUDY QUESTIONS

Choose the ONE best answer.

27.1A 52-year-old woman has a history of rheumatoid arthritis, diabetes, hypertension, and heartburn. Her medications include methotrexate, prednisone, metformin, hydrochlorothiazide, lisinopril, and calcium carbonate. She is worried about the risk of osteoporosis as she approaches menopause. Which of her medications is most likely to contribute to the risk of developing osteoporosis?

A. Calcium carbonate
B. Hydrochlorothiazide

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C. Lisinopril
D. Prednisone

Correct answer = D. Glucocorticoids (for example, prednisone at a dose of ≥5 mg per day for greater than 3 months) are a significant risk factor for osteoporosis. The other medications have not been shown to increase the risk of osteoporosis, and calcium carbonate and hydrochlorothiazide (diuretic that increases calcium retention) may be beneficial for patients at risk of osteoporosis.

27.2 Which of the following is correct regarding the pharmacokinetics of the bisphosphonates?

A. Bisphosphonates are well absorbed after oral-administration.
B. Food or other medications greatly impair absorption of bisphosphonates.
C. Bisphosphonates are mainly metabolized via the cytochrome P450 system.
D. Elimination half-life of bisphosphonates ranges from 4 to 6 hours.

Correct answer = B. Food and other medications decrease absorption of bisphosphonates, which are already poorly absorbed (<1%) after oral administration. Bisphosphonates are cleared from the plasma by binding to bone and being cleared by the kidney (not metabolized by the CYP450 system). The elimination half-life may be years.

27.3 A 56-year-old woman who has been diagnosed with postmenopausal osteoporosis has no history of fractures and no other pertinent medical conditions. Which of the following is most appropriate for management of her osteoporosis?

A. Alendronate
B. Calcitonin
C. Romosozumab
D. Raloxifene

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Correct answer = A. Bisphosphonates are first-line therapy for osteoporosis in postmenopausal women without contraindications. Raloxifene is an alternative that may be less efficacious (especially for nonvertebral and hip fractures) and should only be used in women unable to take bisphosphonates or denosumab. Calcitonin is not recommended. Romosozumab is best used for patients at high risk of fractures.

27.4 A patient has been taking alendronate for postmenopausal osteoporosis for 5 years with a slight increase in bone mineral density and no occurrence of fractures. Risk of which adverse effect might warrant consideration of a drug holiday from alendronate in this patient?

A. Atypical femur fractures
B. Hypercalcemia
C. Osteosarcoma
D. Rhinitis

Correct answer = A. Atypical femur fractures are associated with long-term use of bisphosphonates (greater than 5 years). Therefore, a drug holiday might be considered since the patient has had no fractures. Hypercalcemia and osteosarcoma are associated with the parathyroid hormone analogs, and rhinitis is associated with intranasal calcitonin.

27.5 Which of the following best describes the mechanism of action of denosumab in the treatment of osteoporosis?

A. Parathyroid hormone analog
B. RANKL inhibitor
C. Selective estrogen receptor modulator
D. Sclerostin inhibitor

Correct answer = B. Denosumab is a monoclonal antibody that targets receptor activator of nuclear factor kappa-B ligand (RANKL) and inhibits osteoclast formation and function. Teriparatide and abaloparatide are parathyroid agents, raloxifene is a SERM, and romosozumab is a sclerostin inhibitor.

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27.6 Use of which agent for osteoporosis should be limited to no more than 2 years?

A. Calcitonin
B. Denosumab
C. Teriparatide
D. Zoledronic acid

Correct answer = C. Use of the recombinant parathyroid hormone, teriparatide, should be limited to 2 years. Use beyond 2 years has not been studied and is not recommended. The other agents do not have such limitations.

27.7 Which of the following characteristics would make a patient the most appropriate candidate for abaloparatide treatment for postmenopausal osteoporosis?

A. Fear of needles
B. Desire for once-monthly therapy
C. History of multiple vertebral fractures
D. T-score of −2.0 and no history of fractures

Correct answer = C. Abaloparatide, an analog of parathyroid hormone–related peptide, is best used in patients with a high risk of fractures, such as those with a history of multiple vertebral fractures. Abaloparatide is administered via subcutaneous injection daily. Patients with a T-score indicating osteopenia and no history of fractures may or may not require pharmacotherapy depending on the risk of future fractures.

27.8 A 55-year-old man is diagnosed with Paget disease. He has no other significant medical history. Which agent would be most appropriate for treatment of Paget disease in this patient?

A. Abaloparatide
B. Denosumab
C. Raloxifene
D. Zoledronic acid

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Correct answer = D. Zoledronic acid is the preferred agent for treatment of Paget disease because of its efficacy and once-yearly administration. The other agents do not have an indication for Paget disease.

27.9 A 67-year-old woman complains of severe back pain and is found to have multiple vertebral fractures related to osteoporosis. The patient has a past medical history of hypertension, chronic kidney disease, and a myocardial infarction 6 months ago. Which of the following would exclude the use of romosozumab in this patient?

A. Chronic kidney disease
B. Hypertension
C. Myocardial infarction
D. Vertebral fractures

Correct answer = C. Romosozumab should be avoided in patients with a history of myocardial infarction (especially recent myocardial infarction), as a small but significant increase in myocardial infarction and stroke occurred in clinical studies. Multiple vertebral fractures is a reason to consider (not exclude) therapy with romosozumab. Hypertension and renal dysfunction are not contraindications for use of this agent.

27.10 A 55-year-old woman with postmenopausal osteoporosis has a past medical history of alcohol use disorder, alcoholic liver disease, erosive esophagitis, and hypothyroidism. Which is the primary reason oral bisphosphonates should be used with caution in this patient?

A. Age
B. Erosive esophagitis
C. Liver disease
D. Thyroid disease

Correct answer = B. Bisphosphonates are known to cause esophageal irritation and should be used with caution in a patient with a history of erosive esophagitis. Age is not a factor for consideration in bisphosphonate use. Liver

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disease is not a contraindication to bisphosphonate use, since bisphosphonates are mainly cleared via the kidney. Thyroid disease is not a contraindication to bisphosphonate use, although overaggressive replacement of thyroid may contribute to osteoporosis.

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Unit VI:
Chemotherapeutic Drugs

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28

Principles of Antimicrobial Therapy

Young S. Baek, Eric F. Egelund, Anthony M. Casapao

I. OVERVIEW

Antimicrobial therapy takes advantage of the biochemical differences that exist between microorganisms and human beings. Antimicrobial drugs are effective in the treatment of infections because of their selective toxicity; that is, they have the ability to injure or kill an invading microorganism without harming the cells of the host. In most instances, the selective toxicity is relative rather than absolute, requiring that the concentration of the drug be carefully controlled to target the microorganism, while still being tolerated by the host.

II. SELECTION OF ANTIMICROBIAL AGENTS

Selection of the most appropriate antimicrobial agent requires knowledge of (1) the identity of the microorganism, (2) the susceptibility of the microorganism to a particular agent, (3) the site of the infection, (4) patient factors, (5) the safety and efficacy of the antimicrobial, and (6) the cost of therapy. However, most patients require empiric antimicrobial therapy (immediate administration of the drug(s) prior to bacterial identification and susceptibility testing). Antimicrobial therapy is subsequently adjusted if needed, once the infecting microorganism is identified.

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A. Identification of the infecting microorganism

Characterization of the microorganism is central to the selection of appropriate antimicrobial therapy. A rapid assessment of the nature of the pathogen can sometimes be made based on the Gram stain, which is particularly useful in identifying the presence and morphologic features of microorganisms in body fluids that are normally sterile (blood, cerebrospinal fluid [CSF], pleural fluid, synovial fluid, peritoneal fluid, and urine). However, it is generally necessary to culture the infective microorganism to arrive at a definitive diagnosis and determine its susceptibility to antimicrobial agents. Thus, it is essential to obtain a sample culture of the microorganism prior to initiating treatment with antimicrobials. Otherwise, it is impossible to differentiate whether a negative culture is due to the absence of microorganisms or is a result of antimicrobial effects of administered antibiotics. Definitive identification of the infecting microorganism may require other laboratory techniques, such as direct detection of microbial antigens, DNA, or RNA specific for the microorganism, or identification of an inflammatory or host immune response to the microorganism (Figure 28.1). Detection of microbial RNA or DNA utilizing rapid polymerase chain reaction (PCR) and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry offers accurate, rapid, and cost-effective identification of the infecting microorganism(s). The use of such methods allows for rapid initiation of antimicrobials. However, these methods are not yet available at all institutions. Of note, culture results may not be available at the time of initiation of antimicrobial therapy; however, this should not deter clinicians from initiating empiric antimicrobial therapy.

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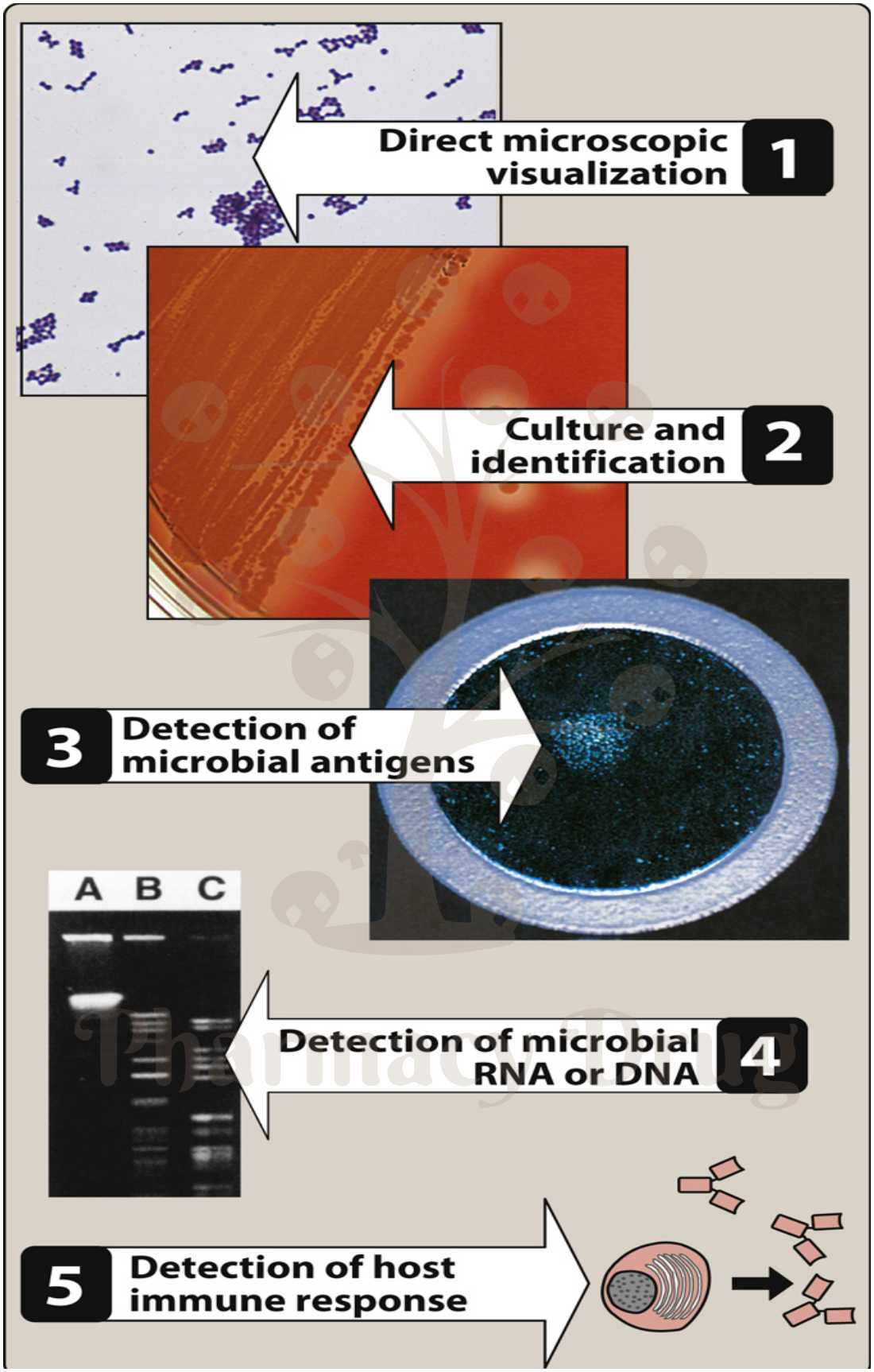

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Figure 28.1 Some laboratory techniques are useful in the diagnosis of microbial diseases.

Clinical Application 28.1: Identification of Antimicrobial Resistant Genes

Detecting microbial RNA or DNA with rapid PCR can be crucial for the initiation of empiric antibiotic therapy. Detection or diagnosis of infection with *methicillin*-resistant *Staphylococcus aureus* (MRSA) is commonly performed by detecting the *mecA* gene through PCR testing. This gene encodes for an altered penicillin-binding protein, PBP-2a, which renders most β-lactam antibiotics ineffective (exception is *ceftaroline*). Positive detection of the *mecA* gene via PCR informs clinicians to initiate or continue the appropriate empiric antibiotics of choice, such as *vancomycin*, while confirming susceptibility of the organism.

B. Empiric antimicrobial therapy

Ideally, the antimicrobial agent used to treat an infection is selected after the microorganism has been identified and its susceptibility to antimicrobial agents established. However, in many cases, results of blood cultures or other laboratory analyses may not be available for a few days, and empiric antimicrobial therapy must be initiated. For example, in the critically ill patient, a delay in treatment could prove fatal, and immediate empiric therapy is indicated.

1. Timing: Acutely ill patients with infections of unknown origin—for example, a neutropenic patient (one who is at risk for infections due to a reduction in neutrophils) or a patient with meningitis (acute inflammation of the membranes covering the brain and spinal cord)—require immediate treatment. For patients with sepsis and hypotension, antimicrobials should be initiated within 1 hour of diagnosis. If possible, therapy should be initiated after specimens for

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culture and other laboratory analyses have been obtained, but before the results of the culture and sensitivity are available.

2.Selection of empiric therapy: Drug choice in the absence of susceptibility data is influenced by the site of infection (that is, which microorganism(s) is/are most likely to cause infection at the suspected site of infection; Figure 28.2), the patient history (for example, previous infections, age, recent travel history, recent antimicrobial therapy, immune status, whether the infection was hospital- or community-acquired), and local susceptibility data. [Note: An antibiogram is a summary profile of the local susceptibility patterns of microorganisms to various antimicrobials. Clinicians use the antibiogram to guide the selection of empiric therapy.] Broad-spectrum therapy may be indicated initially when the microorganism is unknown or polymicrobial infections are likely. The choice of agent(s) may also be guided by a known association of particular microorganisms in a given clinical setting. For example, gram-positive cocci in the spinal fluid of a newborn are unlikely to be Streptococcus pneumoniae and most likely to be Streptococcus agalactiae (a group B streptococci), which is sensitive to *penicillin G.* By contrast, gram-positive cocci in the spinal fluid of a 40-year-old patient are most likely to be S. pneumoniae. This microorganism is frequently resistant to *penicillin G* and often requires treatment with a high-dose third-generation cephalosporin (such as *ceftriaxone*) or *vancomycin*.

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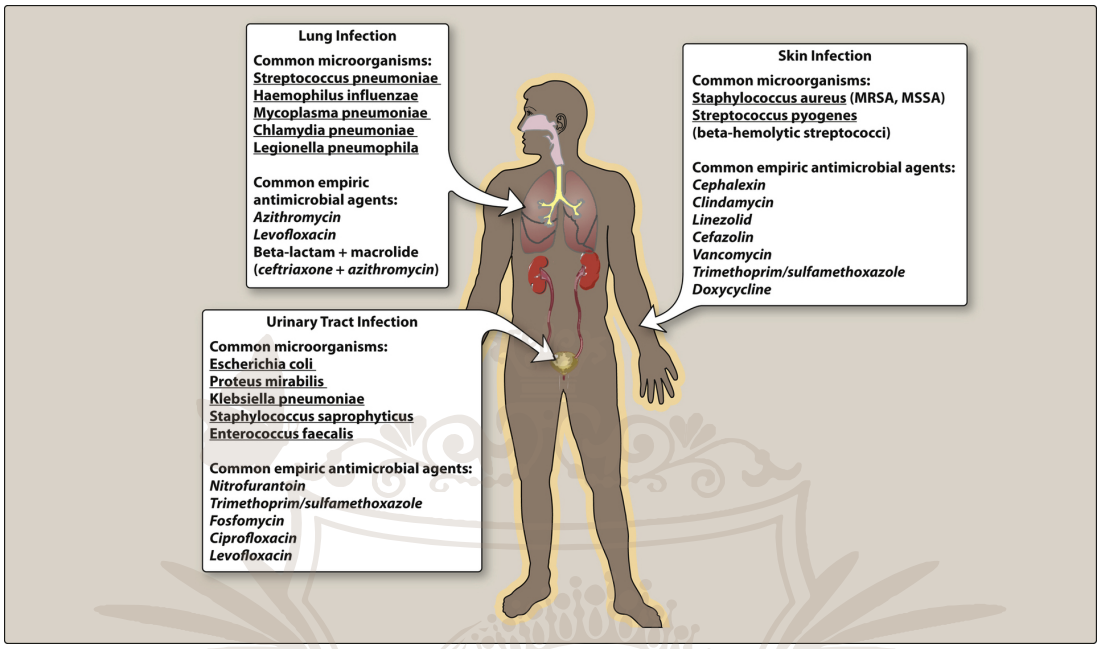

Figure 28.2 Common microorganisms by site of infection.MRSA, *methicillin*-resistant *Staphylococcus aureus*; MSSA, *methicillin*-sensitive *Staphylococcus aureus*.

C. Determination of antimicrobial susceptibility

After a pathogen is isolated and identified by genus and species, its susceptibility to specific antimicrobials serves as a guide in the selection of therapy. Some pathogens, such as Streptococcus pyogenes and Neisseria meningitidis, usually have predictable susceptibility patterns to certain antimicrobials. In contrast, most pathogens, for example, gram-negative bacilli, may show unpredictable susceptibility patterns and require susceptibility testing to determine appropriate antimicrobial therapy. The minimum inhibitory and bactericidal concentrations are used in determining the susceptibility of an antimicrobial (Figure 28.3).

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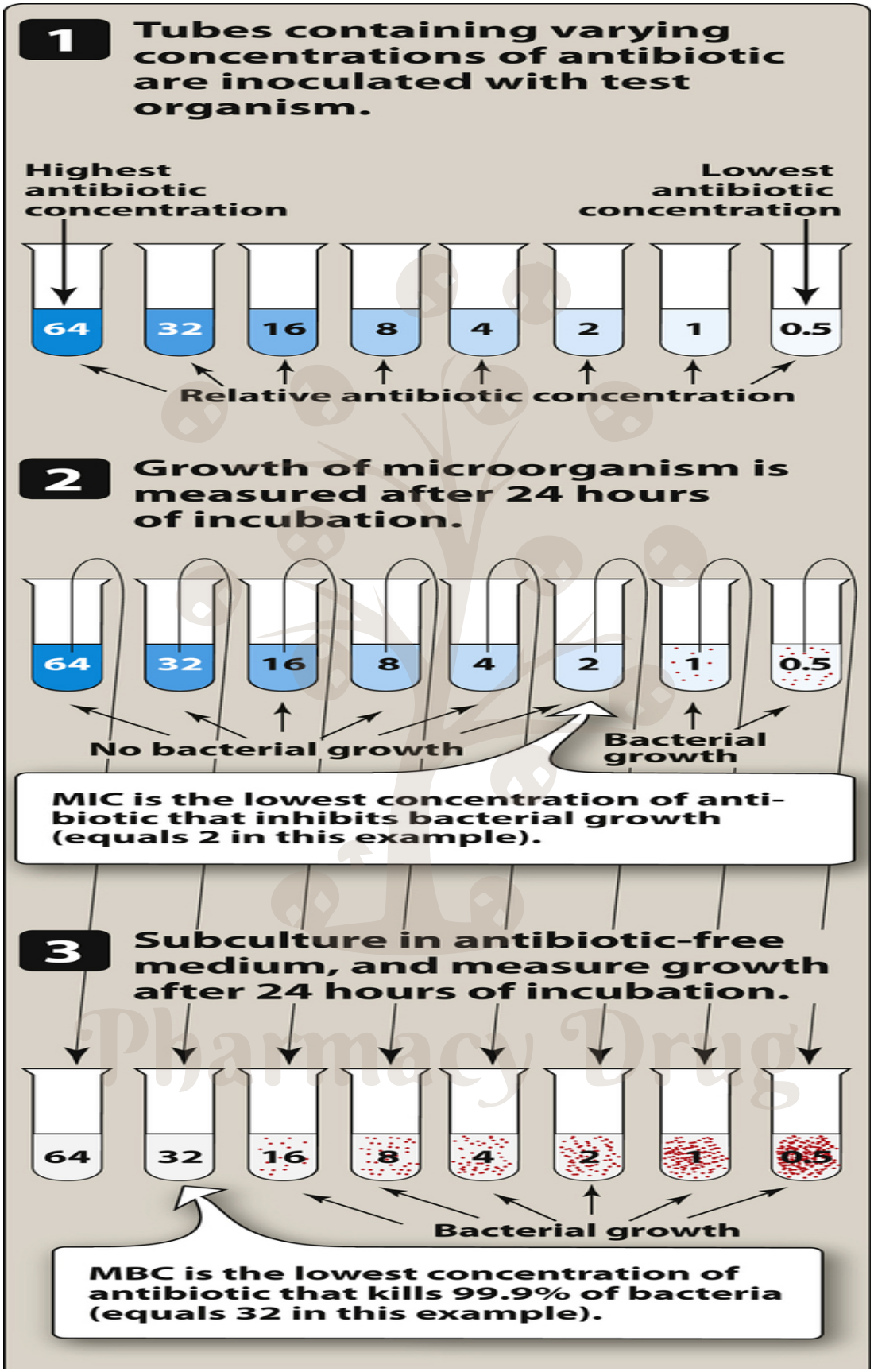

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Figure 28.3 Determination of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of an antibiotic.

1.Bacteriostatic versus bactericidal drugs: Antimicrobial drugs are commonly classified as either bacteriostatic or bactericidal. Historically, bacteriostatic drugs were thought to only arrest the growth and replication of bacteria at drug levels achievable in the patient, whereas bactericidal drugs were able to effectively kill ≥99.9% (3-log reduction) of the infecting microorganism within 18 to 24 hours of incubation under specific laboratory conditions. There is a growing consensus that this classification may be too simplistic, as most bacteriostatic agents can effectively kill microorganisms; however, they are unable to meet the arbitrary cutoff value in the bactericidal definition. Figure 28.4 shows a laboratory experiment in which a bactericidal agent is compared to a bacteriostatic agent and a control. Note that the rate of in vitro killing is greater with bactericidal agents, but both agents can effectively kill the microorganism. It is also possible for an antimicrobial to be bacteriostatic for one microorganism and bactericidal for another. For example, *linezolid* is bacteriostatic against Staphylococcus aureus and enterococci, but is bactericidal against most strains of S. pneumoniae. In addition, recent data have demonstrated that bactericidal and bacteriostatic agents have similar efficacy for treating common clinical infections. In the end, other factors may have a greater impact, including the host immune system, drug concentration at the site of infection, and underlying severity of the illness.

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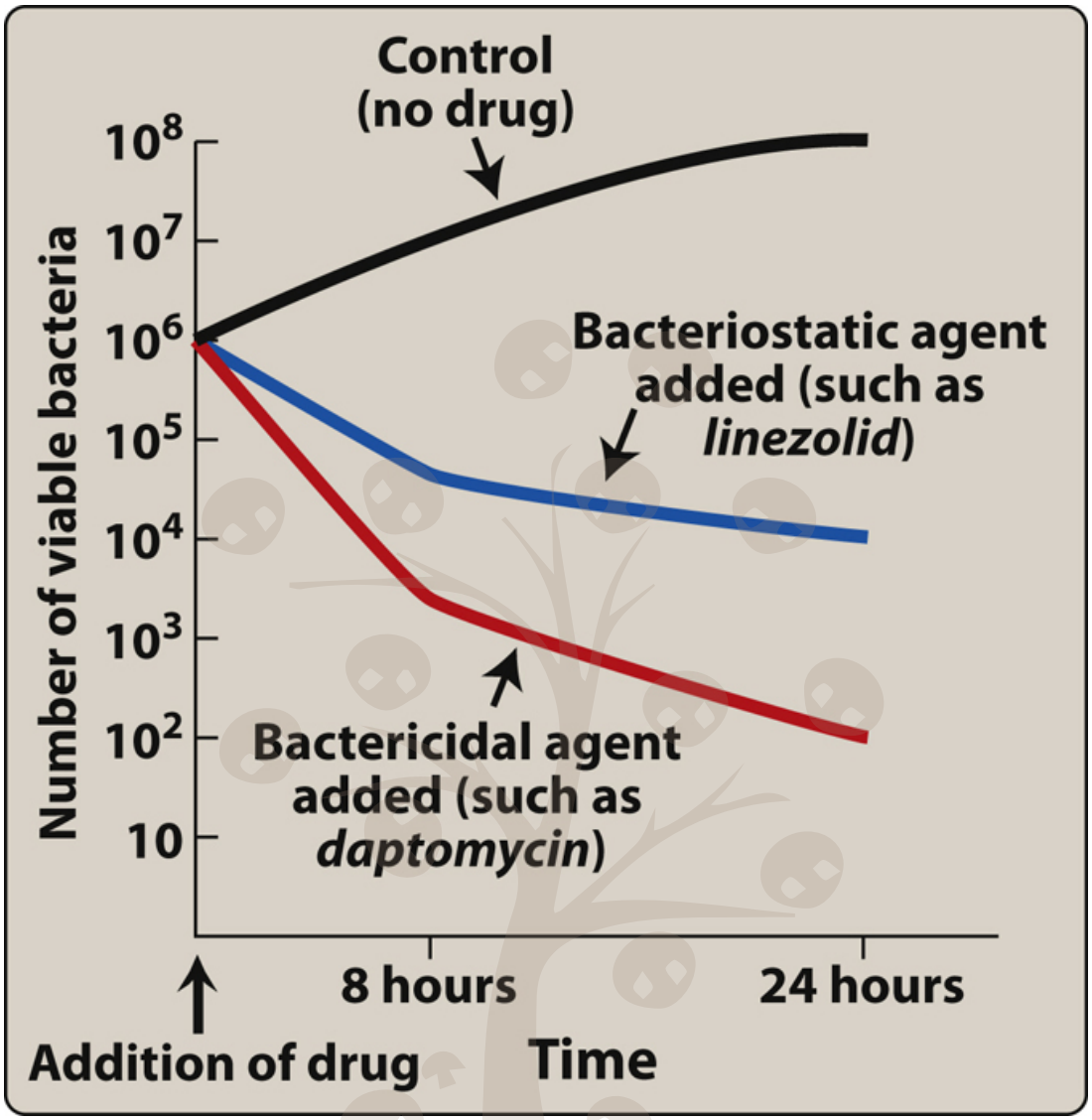

Figure 28.4 Effects of bactericidal and bacteriostatic drugs on the growth of bacteria in vitro.

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2.Minimum inhibitory concentration: The minimum inhibitory concentration (MIC) is the lowest antimicrobial concentration that prevents the visible growth of a microorganism after 24 hours of incubation. This serves as a quantitative measure of in vitro susceptibility and is commonly used in practice to streamline therapy. Computer automation has improved the accuracy and decreased the turnaround time

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for determining MIC results and is the most common approach used by clinical laboratories.

3. **Minimum bactericidal concentration:** The minimum bactericidal concentration (MBC) is the lowest concentration of antimicrobial agents that results in a 99.9% decline in colony count after overnight broth dilution incubations (Figure 28.3). [Note: The MBC is rarely determined in clinical practice due to the time and labor requirements.]

D. Effect of the site of infection on therapy

Adequate levels of an antibiotic must reach the site of infection for the invading microorganisms to be effectively eradicated. Capillaries with varying degrees of permeability carry drugs to the body tissues. Natural barriers to drug delivery are created by the structures of the capillaries of some tissues, such as the prostate, testes, placenta, the vitreous body of the eye, and the central nervous system (CNS). Of particular significance are the capillaries in the brain, which help to create and maintain the blood–brain barrier. This barrier is formed by the single layer of endothelial cells fused by tight junctions that impede entry from the blood to the brain of virtually all molecules, except those that are small and lipophilic. While there are many clinically important sites of infection (for example, CNS, lung, urinary tract, skin), management of infections of the CNS requires special consideration of factors that affect the penetration and concentration of an antimicrobial agent in the CSF. These factors are outlined below.

1. **Lipid solubility:** The lipid solubility of a drug is a major determinant of its ability to penetrate the blood–brain barrier. Lipid-soluble drugs, such as *chloramphenicol* and *metronidazole*, have significant penetration into the CNS, whereas β-lactam antibiotics, such as *penicillin*, are ionized at physiologic pH and have low lipid solubility. Therefore, they have limited penetration through the intact blood–brain barrier

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under normal circumstances. In infections such as meningitis in which the brain becomes inflamed, the barrier does not function as effectively, and local permeability is increased. Some β-lactam antibiotics can enter the CSF in therapeutic amounts when the meninges are inflamed.

2. **Molecular weight:** A drug with low molecular weight has an enhanced ability to cross the blood–brain barrier, whereas compounds with a high molecular weight (for example, *vancomycin*) penetrate poorly, even in the presence of meningeal inflammation.

3. **Protein binding:** A high degree of protein binding of a drug restricts its entry into the CSF. Therefore, the amount of free (unbound) drug in serum, rather than the total amount of drug present, is important for CSF penetration.

4. **Susceptibility to transporters or efflux pumps:** Antibiotics that have an affinity for transporter mechanisms or do not have an affinity for efflux pumps have better CNS penetration.

E. Patient factors

In selecting an antimicrobial, the condition of the patient must be taken into consideration. For example, the status of the immune system, kidneys, liver, circulation, and age must be considered. In women, pregnancy or breastfeeding also affects the selection of an antimicrobial agent.

1. **Immune system:** Elimination of infecting microorganisms from the body is highly dependent on an intact immune system, and the host defense system must ultimately eliminate the invading microorganisms. Alcohol use disorder, diabetes, HIV infection, malnutrition, autoimmune diseases, pregnancy, advanced age, and immunosuppressive drugs can affect immunocompetence. High doses of bactericidal agents or

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longer courses of treatment may be required to eliminate infective microorganisms in these individuals.

2.Renal dysfunction: Poor kidney function may cause the accumulation of certain antimicrobials. Dosage adjustment prevents drug accumulation and adverse effects. Serum creatinine levels are frequently used as an index of renal function for adjustment of drug regimens. However, direct monitoring of serum levels of some antimicrobials (for example, *vancomycin* and the aminoglycosides *amikacin*, *gentamicin*, *tobramycin*) is preferred to identify maximum and/or minimum values and prevent potential toxicities. [Note: The number of functional nephrons decreases with age. Thus, elderly patients are particularly vulnerable to the accumulation of drugs eliminated by the kidneys, even with normal serum creatinine levels.]

3.Hepatic dysfunction: Antimicrobials that are concentrated or eliminated by the liver (for example, *rifampin* and *doxycycline*) must be used with caution when treating patients with liver dysfunction.

4.Poor perfusion: Decreased circulation to an anatomic area, such as the lower limbs of a patient with diabetes, reduces the amount of antimicrobial that reaches that site of infection, making it more difficult to treat. Decreased perfusion of the gastrointestinal (GI) tract may result in reduced absorption, making the attainment of therapeutic concentrations more difficult with oral routes.

5.Age: Renal or hepatic elimination processes are often poorly developed in newborns, making neonates particularly vulnerable to the toxic effects of agents such as *chloramphenicol* and sulfonamides. Young children should not be treated with tetracyclines or fluoroquinolones which affect bone growth and joints, respectively. Elderly patients may

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have decreased renal or liver function, which may alter the pharmacokinetics of certain antimicrobials.

6.Pregnancy and lactation: Many antimicrobials cross the placental barrier or pass into the breast milk and may affect the nursing infant. Prior to prescribing a drug for a pregnant or lactating woman, prescribers should consult the product labeling to review the risk summary and clinical considerations for use in pregnancy and lactation. Although the concentration of an antimicrobial in the fetal circulation or breast milk is usually low, the total dose to the infant may be sufficient to produce detrimental effects. Some antimicrobial agents, such as fluoroquinolones, tetracyclines, sulfonamides, and aminoglycosides, are avoided in pregnancy due to their potential teratogenicity. For example, congenital abnormalities have been reported after administration of tetracyclines to pregnant women, and these agents should generally be avoided in pregnancy due to the risk to the fetus. In addition, *trimethoprim/sulfamethoxazole* can cause kernicterus (brain damage caused by the accumulation of bilirubin in the brain) in the newborn when administered close to the end of pregnancy. Antimicrobial agents such as *doxycycline* cross into the breastmilk and may be associated with a risk of hypoplasia of tooth enamel or tooth discoloration in the nursing infant.

7.Risk factors for multidrug-resistant organisms: Infections with multidrug-resistant pathogens need broader antimicrobial coverage when initiating empiric therapy. Common risk factors for infection with these pathogens include prior antimicrobial therapy in the preceding 90 days, hospitalization for greater than or equal to 2 days within the preceding 90 days, residency in a nursing home or extended-care facility, home infusion therapy and wound care, chronic dialysis within 30 days, family member with multidrug-resistant microorganisms, and immunosuppression.

F. Safety of the agent

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β-Lactam antibiotics are among the least toxic of all antimicrobial drugs because they interfere with a site or function unique to the growth of microorganisms. Other antimicrobial agents (for example, *chloramphenicol*) have less specificity and are reserved for life-threatening infections because of the potential for serious toxicity to the patient. [Note: Safety is related not only to the inherent nature of the drug but also to the patient factors described above that can predispose to toxicity.] Patients taking antimicrobials may not commonly experience adverse drug reactions; however, the list of adverse effects is presented in the product labeling of the drug to inform of the possible risk. For example, an adverse effect of *vancomycin* that many clinicians are aware of is nephrotoxicity. However, only 5% of patients that receive *vancomycin* experience nephrotoxicity. If other medications with a risk for nephrotoxicity are administered concomitantly, then the patient may be at a higher risk of experiencing the reaction. For example, the combination of an aminoglycoside antibiotic and *vancomycin* therapy may pose a higher risk of nephrotoxicity.

G. Cost of therapy

It is common for several drugs to show similar efficacy in treating an infection but vary widely in cost. For example, treatment of MRSA generally includes one of the following: *vancomycin*, *clindamycin*, *daptomycin*, or *linezolid.* Although the choice of therapy usually centers on the site of infection, the severity of the illness, and the ability to take oral medications, it is also important to consider the cost of the medication. The cost of therapy can be limited by transitioning the patient from intravenous (IV) to oral therapy when appropriate.

III. ROUTE OF ADMINISTRATION

The oral route of administration is appropriate for mild infections that can be treated on an outpatient basis. Oral agents have varying

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degrees of bioavailability (Figure 28.5). Parenteral administration is used for drugs that are poorly absorbed from the GI tract and for treatment of patients with serious infections who require maintenance of higher serum concentrations of antimicrobial agents. In hospitalized patients requiring IV therapy, the switch to oral agents should occur as soon as possible. Switching patients from IV to oral therapy when clinically stable has been shown to decrease healthcare costs, shorten the length of stay, and decrease complications from IV catheters. However, some antimicrobials, such as *vancomycin* and aminoglycosides, are poorly absorbed from the GI tract and do not achieve adequate serum levels via oral administration.

ORAL BIOAVAILABILITY	ANTIMICROBIAL AGENTS
Excellent (>90%)	***Clindamycin*** ***Fluconazole*** ***Metronidazole*** ***Trimethoprim-sulfamethoxazole*** ***Doxycycline*** ***Linezolid*** ***Levofloxacin***
Good (60-90%)	***Amoxicillin*** ***Cefepime*** ***Cefaclor*** ***Cephalexin*** ***Ciprofloxacin*** ***Nitrofurantoin*** ***Azithromycin***
Poor (<60%)	***Vancomycin*** ***Acyclovir*** ***Cefdinir*** ***Fosfomycin***

Figure 28.5 Oral bioavailability of antimicrobial agents.

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IV. DETERMINANTS OF RATIONAL DOSING

The rational dosing of antimicrobial agents is based on the pharmacodynamic (the relationship of drug concentrations to antimicrobial effects) and pharmacokinetic properties (absorption, distribution, metabolism, and elimination) of the drug. Three important properties that have a significant influence on the frequency of dosing are concentration-dependent killing, time-dependent (concentration-independent) killing, and postantibiotic effect (PAE). Utilizing these properties to optimize antimicrobial dosing regimens can improve clinical outcomes and possibly decrease the development of resistance.

A. Concentration-dependent killing

Certain antimicrobial agents, including aminoglycosides and *daptomycin*, show a significant increase in the rate of bacterial killing as the concentration of antimicrobial increases from four-fold to 64-fold the MIC of the drug for the infecting microorganism (Figure 28.6A). Giving drugs that exhibit this concentration-dependent killing by a once-a-day bolus infusion achieves high peak levels, favoring rapid killing of the infecting pathogen.

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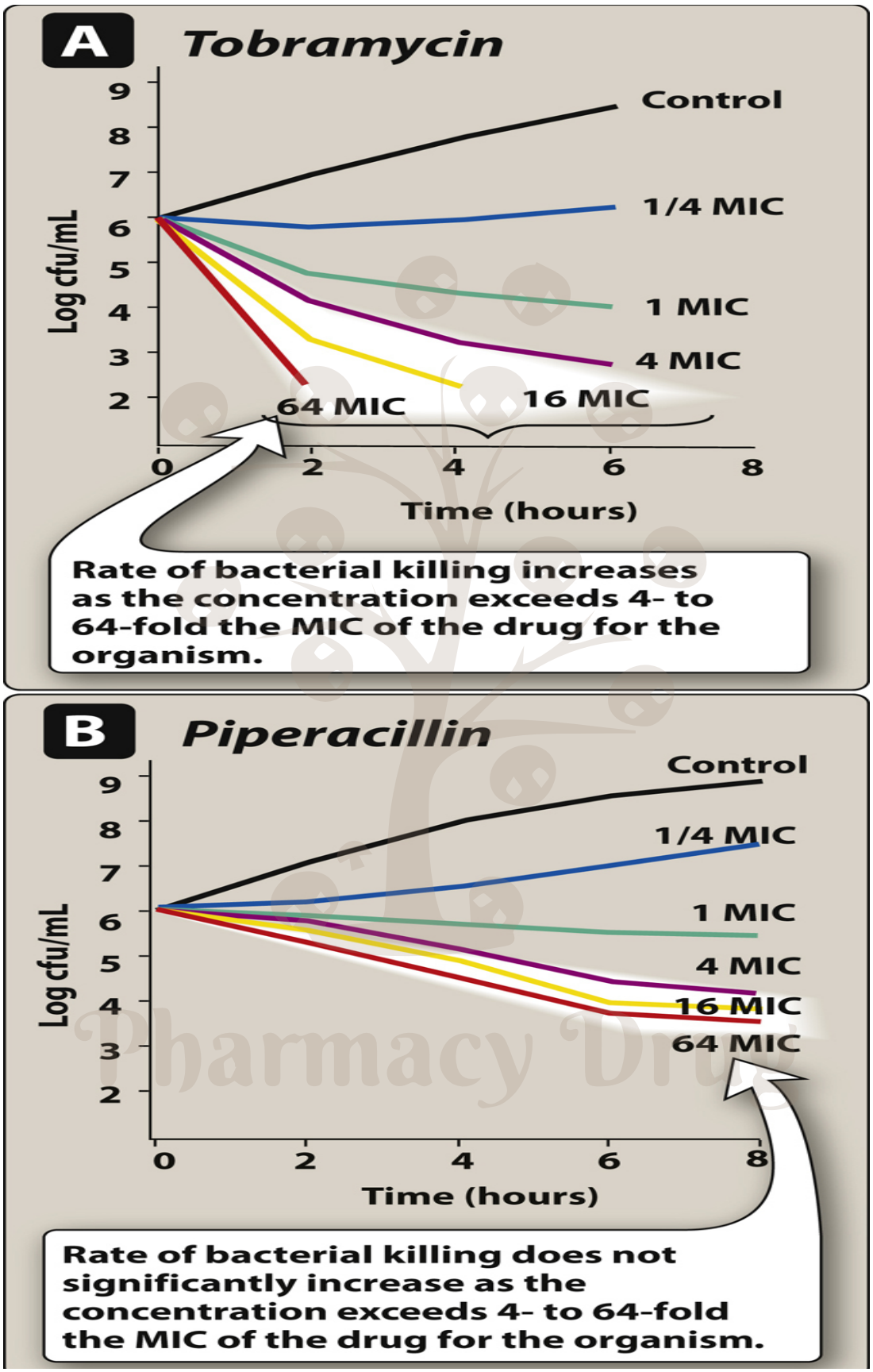

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Figure 28.6 **A.** Significant dose-dependent killing effect shown by *tobramycin.* **B.** Nonsignificant dose-dependent killing effect shown by *piperacillin.* CFU = colony-forming units; MIC = minimum inhibitory concentration.

B. Time-dependent (Concentration-independent) killing

In contrast, β-lactams, macrolides, *clindamycin*, and *linezolid* do not exhibit concentration-dependent killing (Figure 28.6B). The clinical efficacy of these antimicrobials is best predicted by the percentage of time that blood concentrations of a drug remain above the MIC. This effect is sometimes called time-dependent (or concentration-independent) killing. For example, dosing schedules for the penicillins and cephalosporins that ensure blood levels greater than the MIC for 50 and 60% of the time, respectively, provide the most clinical efficacy. Therefore, extended (generally 3-4 hours) or continuous (24 hours) infusions can be utilized instead of intermittent bolus dosing (generally administered over 30 minutes) to achieve prolonged time above the MIC and kill more bacteria. Other drugs, such as fluoroquinolones and *vancomycin*, work best by optimizing the ratio of the 24-hour area under the concentration–time curve to MIC (AUC_{24}/MIC). The AUC_{24} is the overall exposure of a drug during the dosing interval and takes into account the concentration, as well as the time.

C. Postantibiotic effect

The PAE is a persistent suppression of microbial growth that occurs after the level of antimicrobial has fallen below the MIC. Antimicrobial drugs exhibiting a long PAE (for example, aminoglycosides and fluoroquinolones) often require only one dose per day, particularly against gram-negative bacteria.

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V. CHEMOTHERAPEUTIC SPECTRA

In this text, the clinically important bacteria have been organized into eight groups based on Gram stain, morphology, and biochemical or other characteristics. They are represented as a color-coded list (Figure 28.7A). The ninth section of the list is labeled “Other,” and it is used to represent any organism not included in one of the other eight categories. In Figure 28.7B to D, the list is used to illustrate the spectra of bacteria for which a particular antimicrobial is therapeutically effective.

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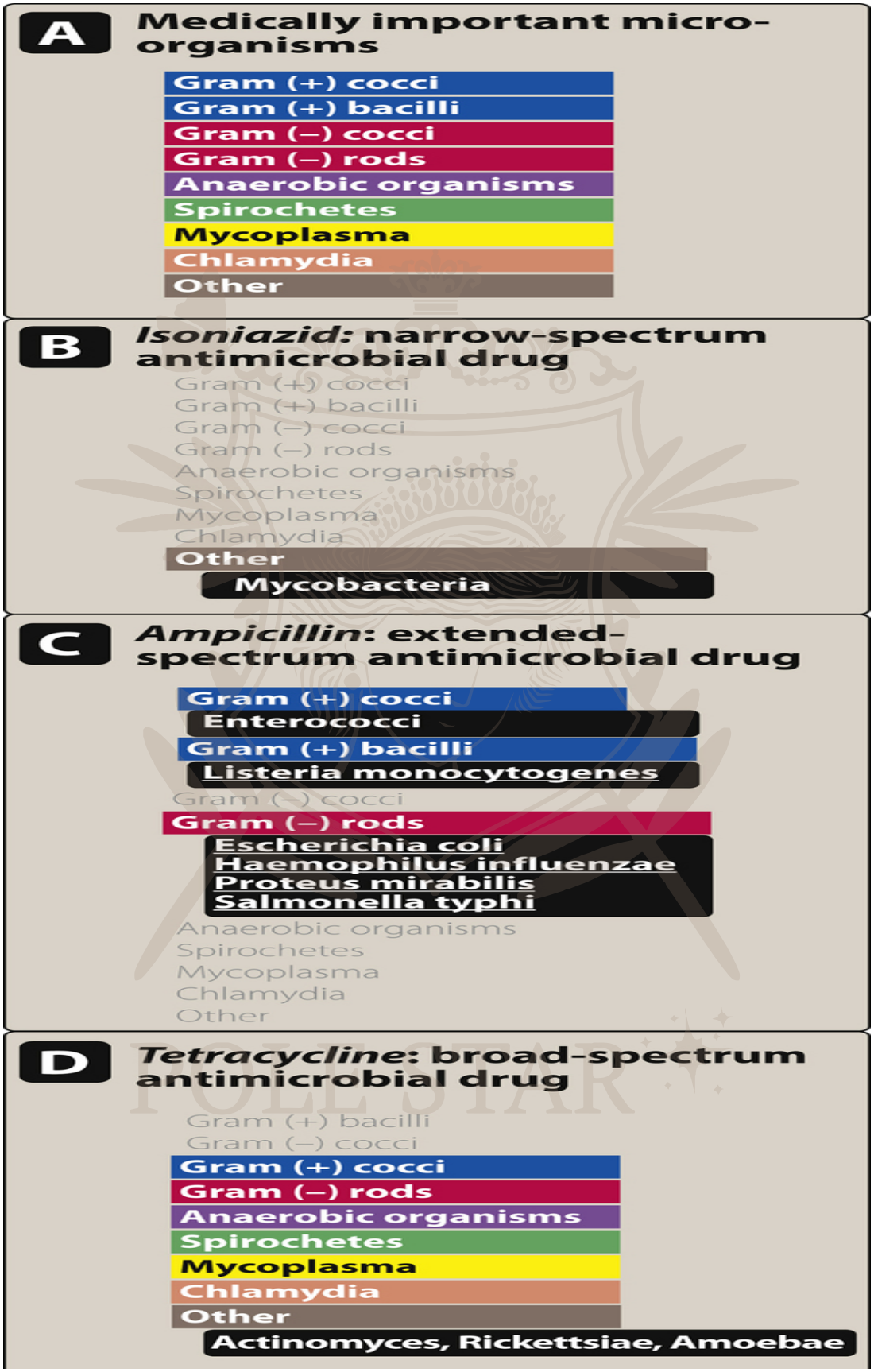
A
Medically important micro-organisms
Gram (+) cocci
Gram (+) bacilli
Gram (–) cocci
Gram (–) rods
Anaerobic organisms
Spirochetes
Mycoplasma
Chlamydia
Other
B
Isoniazid: narrow-spectrum antimicrobial drug
Gram (+) cocci
Gram (+) bacilli
Gram (–) cocci
Gram (–) rods
Anaerobic organisms
Spirochetes
Mycoplasma
Chlamydia
Other
Mycobacteria
C
Ampicillin: extended-spectrum antimicrobial drug
Gram (+) cocci
Enterococci
Gram (+) bacilli
Listeria monocytogenes
Gram (–) cocci
Gram (–) rods
Escherichia coli
Haemophilus influenzae
Proteus mirabilis
Salmonella typhi
Anaerobic organisms
Spirochetes
Mycoplasma
Chlamydia
Other
D
Tetracycline: broad-spectrum antimicrobial drug
Gram (+) bacilli
Gram (–) cocci
Gram (+) cocci
Gram (–) rods
Anaerobic organisms
Spirochetes
Mycoplasma
Chlamydia
Other
Actinomyces, Rickettsiae, Amoebae

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Figure 28.7 **A.** Color-coded representation of medically important microorganisms. **B.** *Isoniazid*, narrow-spectrum antimicrobial agent. **C.** *Ampicillin*, an extended-spectrum antimicrobial agent. **D.** *Tetracycline*, a broad-spectrum antimicrobial agent.

A. Narrow-spectrum antimicrobials

Antimicrobial agents acting only on a single or a limited group of microorganisms are said to have a narrow spectrum. For example, *isoniazid* is active only against Mycobacterium tuberculosis (Figure 28.7B).

B. Extended-spectrum antimicrobials

Extended spectrum is the term applied to antimicrobials that are modified to be effective against gram-positive microorganisms and also against a significant number of gram-negative bacteria. For example, *ampicillin* is considered to have an extended spectrum because it acts against gram-positive and some gram-negative bacteria (Figure 28.7C).

C. Broad-spectrum antimicrobials

Drugs such as *tetracycline*, fluoroquinolones, and carbapenems affect a wide variety of microbial species and are referred to as broad-spectrum antibiotics (Figure 28.7D). Broad-spectrum antibiotics provide coverage of gram-positive as well as gram-negative species and can be used empirically during culture identification and susceptibility testing. Administration of broad-spectrum antimicrobials can drastically alter the nature of the normal bacterial microbiota and precipitate a superinfection due to organisms such as Clostridioides difficile, the growth of which is normally kept in check by the presence of other colonizing microorganisms.

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VI. COMBINATIONS OF ANTIMICROBIAL DRUGS

It is therapeutically advisable to treat patients with a single agent that is most specific to the infecting microorganism. This strategy reduces the possibility of superinfections, decreases the emergence of resistant microorganisms, and minimizes toxicity. However, in some situations, combinations of antimicrobial drugs are advantageous or even required. A combination of antimicrobial agents may be used empirically while culture results are pending. This allows for effective coverage of pathogens common to the site of infection.

A. Advantages of drug combinations

Certain combinations of antibiotics, such as β-lactams and aminoglycosides, show synergy; that is, the combination is more effective than either of the drugs used separately. Because such synergy among antimicrobial agents is rare, synergistic combinations are only indicated in special situations (for example, in the treatment of enterococcal endocarditis). Combinations may also be used when an infection is of unknown origin or when there are microorganisms with variable sensitivity, such as when treating tuberculosis.

B. Disadvantages of drug combinations

Some antimicrobials act only when microorganisms are multiplying. Thus, coadministration of an agent that causes bacteriostasis plus a second agent that is bactericidal may result in the first drug interfering with the action of the second. For example, bacteriostatic tetracycline drugs may interfere with the bactericidal effects of penicillins and cephalosporins. Another concern is the risk of selection pressure and the development of antimicrobial resistance by giving unnecessary combination therapy.

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VII. DRUG RESISTANCE

Bacteria are considered resistant to an antimicrobial if the maximal level of the antimicrobial that can be tolerated by the host does not halt bacterial growth. Some microorganisms are inherently resistant to an antimicrobial. For example, most gram-negative microorganisms are inherently resistant to *vancomycin.* However, microbial species that are normally responsive to a particular drug may develop more virulent or resistant strains through spontaneous mutation or acquired resistance and selection. Some of these strains may even become resistant to more than one antimicrobial.

A. Genetic alterations leading to drug resistance

Acquired antimicrobial resistance requires the temporary or permanent gain or alteration of bacterial genetic information. Resistance develops due to the ability of DNA to undergo spontaneous mutation or to move from one microorganism to another.

B. Altered expression of proteins in drug-resistant microorganisms

Drug resistance is mediated by a variety of mechanisms, such as an alteration in an antimicrobial target site, decreased penetration of the drug due to lower permeability, increased efflux of the drug, or presence of antimicrobial-inactivating enzymes (Figure 28.8).

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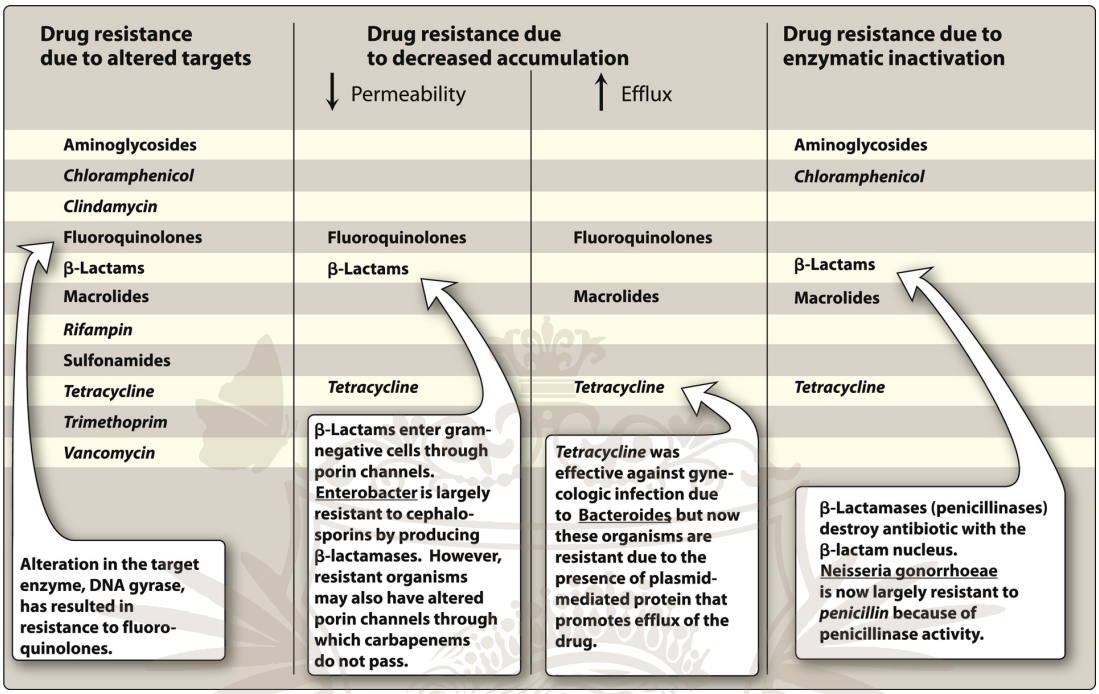

Figure 28.8 Some mechanisms of resistance to antibiotics.

1. Modification of target sites: Alteration of the target site of an antimicrobial through mutation can confer resistance to one or more related antimicrobials. For example, S. pneumoniae resistance to β-lactam antimicrobials involves alterations in one or more of the major bacterial penicillin-binding proteins, resulting in decreased binding of the antimicrobial to its target.

2. Decreased accumulation: Decreased uptake or increased efflux of an antimicrobial can confer resistance because the drug is unable to attain access to the site of its action in sufficient concentrations to injure or kill the microorganism. For example, gram-negative microorganisms can limit the penetration of certain agents, including β-lactam antimicrobials, as a result of an alteration in the number and structure of porins (channels) in the outer membrane. Also, the presence of an efflux pump (pumps drug out of the cell) can

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limit levels of a drug in a microorganism, as seen with tetracyclines.

3. **Enzymatic inactivation:** The ability to destroy or inactivate the antimicrobial agent can also confer resistance to microorganisms. Examples of antimicrobial-inactivating enzymes include (1) β-lactamases ("penicillinases") that hydrolytically inactivate the β-lactam ring of penicillins, cephalosporins, and related drugs; (2) acetyltransferases that transfer an acetyl group to the antimicrobial, inactivating *chloramphenicol* or aminoglycosides; and (3) esterases that hydrolyze the lactone ring of macrolides.

VIII. PROPHYLACTIC USE OF ANTIMICROBIALS

Certain clinical situations, such as dental procedures and surgeries, require the use of antimicrobials for prevention rather than for the treatment of infections (Figure 28.9). Manipulation of gingival tissue during dental procedures can introduce oral microbiota such as Streptococcus spp. into the bloodstream, leading to an infection. In addition, healthcare workers can also introduce skin microbiota such as S. aureus into the bloodstream. This can be a concern because if unmanaged, it can lead to the development of endocarditis in the patient. Prophylactic use of antimicrobial agents can prevent the surgical complication of postsurgical infection. [Note: Oral *amoxicillin* is commonly used for prophylaxis before dental procedures, and intravenous *cefazolin* and *vancomycin* are examples of antimicrobial agents utilized for surgical prophylaxis.] Because the indiscriminate use of antimicrobial agents can result in bacterial resistance and superinfection, prophylactic use is restricted to clinical situations in which the benefits outweigh the potential risks. The duration of prophylaxis should be closely controlled to prevent the unnecessary development of antibiotic resistance.

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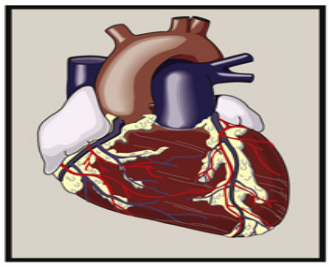
Pretreatment may prevent streptococcal infections in patients with a history of rheumatic heart disease. Patients may require years of treatment.



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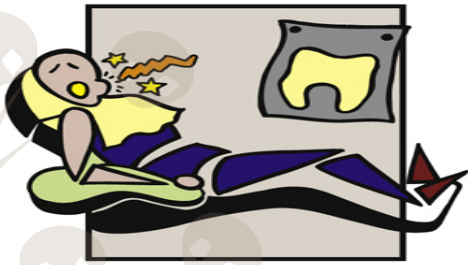
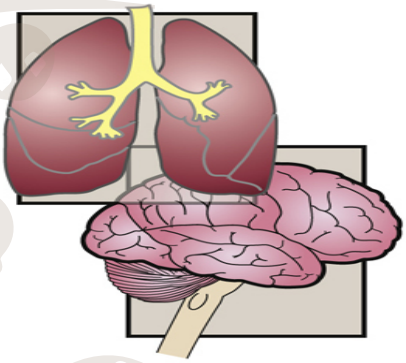
Pretreatment of patients undergoing dental extractions who have implanted prosthetic devices, such as artificial heart valves, prevents seeding of the prosthesis.



3

Pretreatment may prevent tuberculosis or meningitis among individuals who are in close contact with infected patients.



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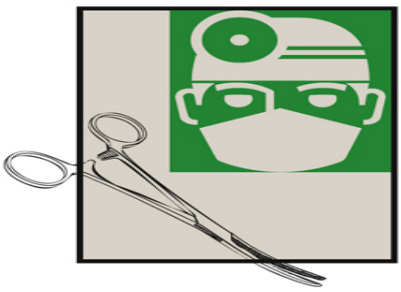
Treatment prior to most surgical procedures can decrease the incidence of infection afterwards. Effective prophylaxis is directed against the most likely organism, not eradication of every potential pathogen.



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potential pathogen.

Figure 28.9 Some clinical situations in which prophylactic antibiotics are indicated.

IX. COMPLICATIONS OF ANTIMICROBIAL THERAPY

Even though antimicrobials are selectively toxic to an invading microorganism, the host may still experience adverse effects. For example, the drug may produce an allergic response or may be toxic in ways unrelated to the antimicrobial activity.

A. Hypersensitivity

Hypersensitivity or immune reactions to antimicrobial drugs or their metabolic products frequently occur. For example, the penicillins, despite their almost absolute selective microbial toxicity, can cause serious hypersensitivity problems, ranging from urticaria (hives) to anaphylactic shock. Some reactions may be related to the rate of infusion, such as "*vancomycin* infusion reaction" seen with rapid infusion of *vancomycin.* Patients with a documented history of Stevens–Johnson syndrome or toxic epidermal necrolysis reaction (a severe sloughing of skin and mucus membranes) to an antimicrobial should *never* be rechallenged, not even for antimicrobial desensitization.

B. Direct toxicity

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High serum concentrations of certain antimicrobials may cause toxicity by directly affecting cellular processes in the host. For example, aminoglycosides can cause ototoxicity by interfering with membrane function in the auditory hair cells. Fluoroquinolones can have effects on cartilage and tendons, and tetracyclines have direct effects on bones. Some antimicrobials can cause photosensitivity (for example, tetracyclines and

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fluoroquinolones). Adverse events and toxicities associated with various antimicrobials are reviewed in Chapters 29 to 36.

X. CLASSIFICATION OF ANTIMICROBIAL AGENTS

Antimicrobial drugs can be classified in a number of ways: (1) by their chemical structure (for example, β-lactams or aminoglycosides), (2) by their mechanism of action (for example, cell wall synthesis inhibitors), or (3) by their activity against particular types of microorganisms (for example, bacteria, fungi, or viruses). Chapters 29 through 31 are organized by the mechanisms of action of the drug (Figure 28.10), and Chapters 32 through 36 are organized according to the type of microorganisms affected by the drug.

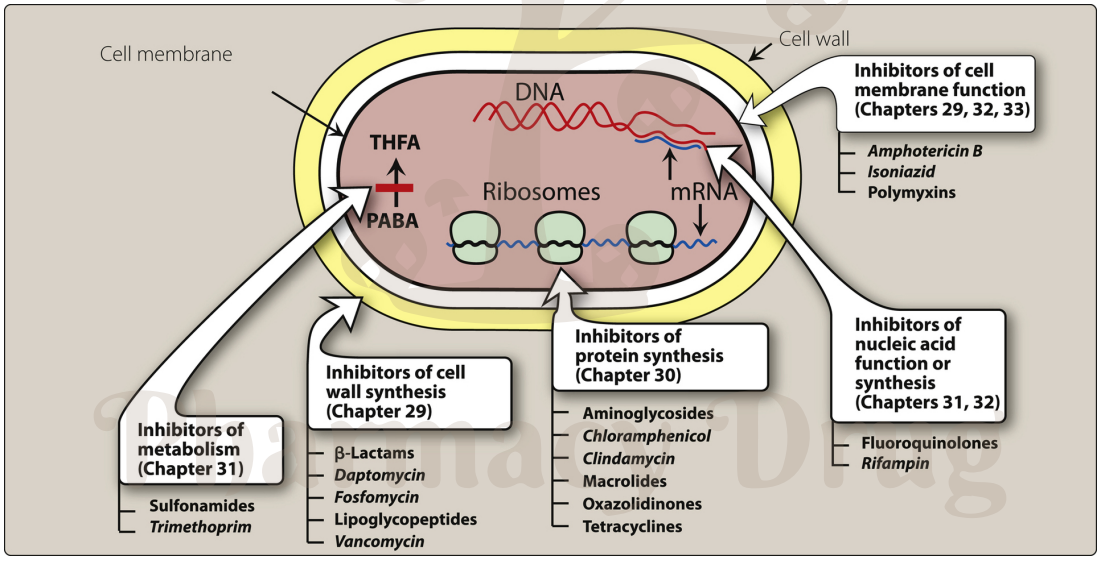

Figure 28.10 Classification of some antimicrobial agents by their sites of action.THFA = tetrahydrofolic acid; PABA = *p*-aminobenzoic acid.

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Chapter Summary

- Antimicrobial selection can be driven by multiple factors: site of infection, type of antimicrobial, the timing of antimicrobial (empiric vs. definitive), patient characteristics, and other principles. One of the most important principles is the identification of the potential microorganisms causing the infection. This can assist in streamlining the selection of the antimicrobial.
- The frequency of dosing of antimicrobials is driven by antimicrobial killing properties, such as concentration-dependent killing, time-dependent killing, and PAE.
- The oral route of administration for antimicrobials is utilized mostly for mild or nonsevere types of infections. The oral route is usually utilized in an outpatient setting or when transitioning from hospitalization to outpatient therapy.
- The spectrum of antimicrobial activity differs by class and within the same class of antimicrobials. Differentiating the coverage by narrow spectrum, extended spectrum, and broad spectrum provides more insight into determining the differences between the antimicrobial classes.
- Antimicrobials that are narrow-spectrum agents provide coverage of a single or limited number of microorganisms.
- Extended-spectrum antimicrobials provide coverage of gram-positive and some gram-negative microorganisms.
- Broad-spectrum antimicrobials are effective against a wide variety of microbial species.
- Combination therapy of antimicrobials has both advantages and disadvantages. It is important to weigh the increased risk of adverse events with the benefits of eradication of a greater spectrum of potential microorganisms.
- Antimicrobial resistance may be developed or intrinsically carried. The mechanisms of resistance vary and include alteration of expressed proteins, modification of target sites, enzymatic inactivation, and decreased accumulation.
- Antimicrobials are usually administered for treatment of an infection, but these agents may be used as prophylaxis in certain scenarios such as dental and surgical procedures.
- Complications of antimicrobials may occur in patients, from hypersensitivity to toxicity.
- Antimicrobials are classified by chemical structure, by mechanism of action, or based on their activity against particular types of microorganisms.

@pharmacy_drug2

STUDY QUESTIONS

Choose the ONE best answer.

28.1 A 56-year-old woman presents with fever, cough, and shortness of breath upon admission. Her chest X-ray shows bilateral infiltrates consistent with pneumonia. Respiratory cultures are pending, and she is initiated on a combination of ceftriaxone and azithromycin. Which of the following best describes the use of ceftriaxone and azithromycin in this case?

A. Concentration-dependent killing therapy
B. Definitive therapy
C. Empiric therapy
D. Prophylactic therapy

Correct answer = C. Empiric therapy is initiated before a causative microorganism is identified. Empiric therapy is designed to cover the most common causative organisms at the site of infection. The combination of ceftriaxone and azithromycin is often used in the empiric treatment of pneumonia, and together the two agents provide coverage of some of the most likely organisms, such as Streptococcus pneumoniae, Haemophilus influenzae, and Mycoplasma pneumoniae. If a microorganism is later identified, the therapy can be adjusted appropriately based on the sensitivities of the organism (definitive therapy). Both the cephalosporin (ceftriaxone) and the macrolide (azithromycin) provide time-dependent killing. Prophylactic therapy is used to prevent infection, rather than treat an active infection.

28.2 When evaluating drug therapy for meningitis, which of the following factors is expected to have the LEAST influence on the penetration and concentration of an antibacterial agent in the cerebrospinal fluid?

A. Lipid solubility of the drug
B. Minimum inhibitory concentration of the drug
C. Protein binding of the drug
D. Molecular weight of the drug

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Correct answer = B. Although the minimum inhibitory concentration impacts the effectiveness of the drug against a given bacteria, it does not affect the ability of a drug to cross the blood–brain barrier. Lipid solubility, protein binding, and molecular weight all determine the likelihood of a drug to penetrate the blood–brain barrier and concentrate in the cerebrospinal fluid.

28.3 Which of the following antimicrobials should be closely monitored in a patient with kidney dysfunction due to the risk of drug accumulation and toxicity?

A. Doxycycline
B. Amikacin
C. Rifampin
D. Tetracycline

Correct answer = B. Amikacin, an aminoglycoside, is primarily eliminated renally. Aminoglycoside therapy should be avoided or used with caution in patients with kidney dysfunction. Drug concentrations should be monitored closely in patients with renal dysfunction. Tetracycline, doxycycline, and rifampin are primarily eliminated via the hepatic route.

28.4 A 24-year-old patient who is in the third trimester of pregnancy presents with urinary frequency, urgency, and fever. She is diagnosed with a urinary tract infection. Which of the following antibiotics is most appropriate to treat the infection in this patient?

A. Trimethoprim/sulfamethoxazole
B. Doxycycline
C. Amoxicillin
D. Gentamicin

POLE STAR

Correct answer = C. Trimethoprim/sulfamethoxazole is avoided in pregnancy due to the risk of kernicterus during the third trimester. Doxycycline is avoided in pregnancy due to the risk of enamel hypoplasia. Aminoglycosides such as gentamicin and amikacin are also avoided due to teratogenic risks. β-Lactams such as amoxicillin are generally considered safe for use in pregnancy.

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28.5 Which of the following antimicrobials exhibits a long postantibiotic effect that permits once-daily dosing?

A. Gentamicin
B. Penicillin G
C. Vancomycin
D. Aztreonam

Correct answer = A. Aminoglycosides, including gentamicin, possess a long postantibiotic effect, especially when given as a high dose every 24 hours. Penicillin G, clindamycin, and vancomycin have a relatively short postantibiotic effect and require dosing that maintains concentrations above the MIC for a longer portion of the dosing interval.

28.6 A patient is infected by a gram-negative organism that is resistant to carbapenems, likely due to altered porin channels. This is an example of what mechanism of drug resistance?

A. Altered targets
B. Decreased accumulation
C. Lipopolysaccharide modification
D. Enzymatic inactivation

Correct answer = B. Gram-negative organisms, in particular, can alter the number or structure of porins, a type of protein channel in their outer membranes, which decrease drug permeability, and leads to decreased accumulation of the drug.

28.7 A 39-year-old patient is scheduled to have a total knee replacement. Which of these antimicrobial agents is most appropriate for surgical prophylaxis to cover microorganisms such as Staphylococcus aureus and Streptococcus pyogenes?

A. Levofloxacin
B. Isoniazid
C. Vancomycin
D. Cefepime

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Correct answer = C. Levofloxacin and cefepime would not be appropriate choices to provide coverage for skin microbiota due to their broader spectrum of activity. Isoniazid is a narrow-spectrum agent preferred for tuberculosis. Vancomycin is an agent of choice, as it provides excellent coverage for skin microbiota such as *Staphylococcus* spp. and *Streptococcus* spp.

28.8 Which of the following adverse drug reactions precludes a patient from being rechallenged with that drug in the future?

A. Itching/rash from penicillin
B. Stevens–Johnson syndrome from sulfamethoxazole/trimethoprim
C. Gastrointestinal (GI) upset from clarithromycin
D. *Clostridioides difficile* superinfection from moxifloxacin

Correct answer = B. Stevens–Johnson syndrome is a severe idiosyncratic reaction that can be life-threatening, and these patients should never be rechallenged with the offending agent. Itching/rash is a commonly reported reaction in patients receiving penicillins but is not life-threatening. A patient may be rechallenged if the benefits outweigh the risk (for example, pregnant patient with syphilis) or the patient could be exposed through a desensitization procedure. GI upset is a common side effect of clarithromycin and it is not severe enough to cause dehydration. Moxifloxacin is a broad-spectrum antibiotic that can inhibit the normal flora of the GI tract, increasing the risk for the development of superinfections like C. difficile. This is not an allergic reaction, and the patient can be rechallenged; however, the patient might be at risk for developing C. difficile infection again.

28.9 During a medication history, a patient mentions that he had a reaction from a drug years ago when he was being treated for a methicillin-resistant Staphylococcus aureus (MRSA) infection. He remembers that the reaction occurred because the medicine was infused too quickly. Which of the following medications most likely caused this reaction?

A. Ampicillin
B. Chloramphenicol
C. Erythromycin

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D. Vancomycin

Correct answer = D. Rapid infusion of vancomycin can cause a hypersensitivity reaction in some patients, known as vancomycin infusion reaction or vancomycin flushing syndrome. The reaction typically consists of pruritus and an erythematous rash covering the face and neck; weakness and angioedema may also occur. Treatment consists of discontinuing vancomycin and administering diphenhydramine.

28.10 Which of the following classes of antimicrobials has a mechanism of action to inhibit cell wall synthesis?

A. Aminoglycosides
B. β-Lactams
C. Macrolides
D. Tetracyclines

Correct answer = B. The β-lactam antimicrobials such as penicillins and cephalosporins act by inhibiting synthesis of the bacterial cell wall. The other drug categories work by inhibiting targeting bacterial ribosomes and inhibiting bacterial protein synthesis (Figure 28.10).

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29

Cell Wall Inhibitors

Veena Venugopalan, Barbara A. Santevecchi

I. OVERVIEW

Some antimicrobial drugs selectively interfere with synthesis of the bacterial cell wall—a structure that mammalian cells do not possess. The cell wall is composed of a polymer called peptidoglycan that consists of glycan units joined to each other by peptide cross-links. To be maximally effective, inhibitors of cell wall synthesis require actively proliferating microorganisms. Figure 29.1 shows the classification of agents affecting cell wall synthesis.

POLE STAR

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PENICILLINS

*Amoxicillin** AMOXIL
*Ampicillin*** GENERIC ONLY
*Dicloxacillin** GENERIC ONLY
Nafcillin GENERIC ONLY
Oxacillin GENERIC ONLY
Penicillin G PFIZERPEN
Penicillin G benzathine BICILLIN L-A
Penicillin G benzathine and penicillin G procaine BICILLIN C-R
*Penicillin V** GENERIC ONLY

CEPHALOSPORINS

*Cefaclor** GENERIC ONLY
*Cefadroxil** GENERIC ONLY
Cefazolin ANCEF, KEFZOL
*Cefdinir** OMNICEF

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Cefepime MAXIPIME
Cefiderocol FETROJA
*Cefixime** SUPRAX
Cefotetan CEFOTAN
Cefoxitin MEFOXIN
*Cefpodoxime** VANTIN
Cefotaxime CLAFORAN
*Cefprozil** CEFZIL
Ceftaroline TEFLARO
Ceftazidime FORTAZ
Ceftriaxone GENERIC ONLY
*Cefuroxime*** CEFTIN, ZINACEF
*Cephalexin** KEFLEX

CARBAPENEMS

Doripenem DORIBAX
Ertapenem INVANZ
Imipenem/cilastatin PRIMAXIN
Meropenem MERREM

MONOBACTAMS

Aztreonam AZACTAM

β-LACTAMASE INHIBITOR + ANTIBIOTIC COMBINATIONS

Avibactam + ceftazidime AVYCAZ
*Clavulanic acid + amoxicillin** AUGMENTIN
Relebactam+imipenem/cilastatin RECARBRIO
Sulbactam + ampicillin UNASYN
Tazobactam + ceftolozane ZERBAXA
Tazobactam + piperacillin ZOSYN
Vaborbactam + meropenem VABOMERE

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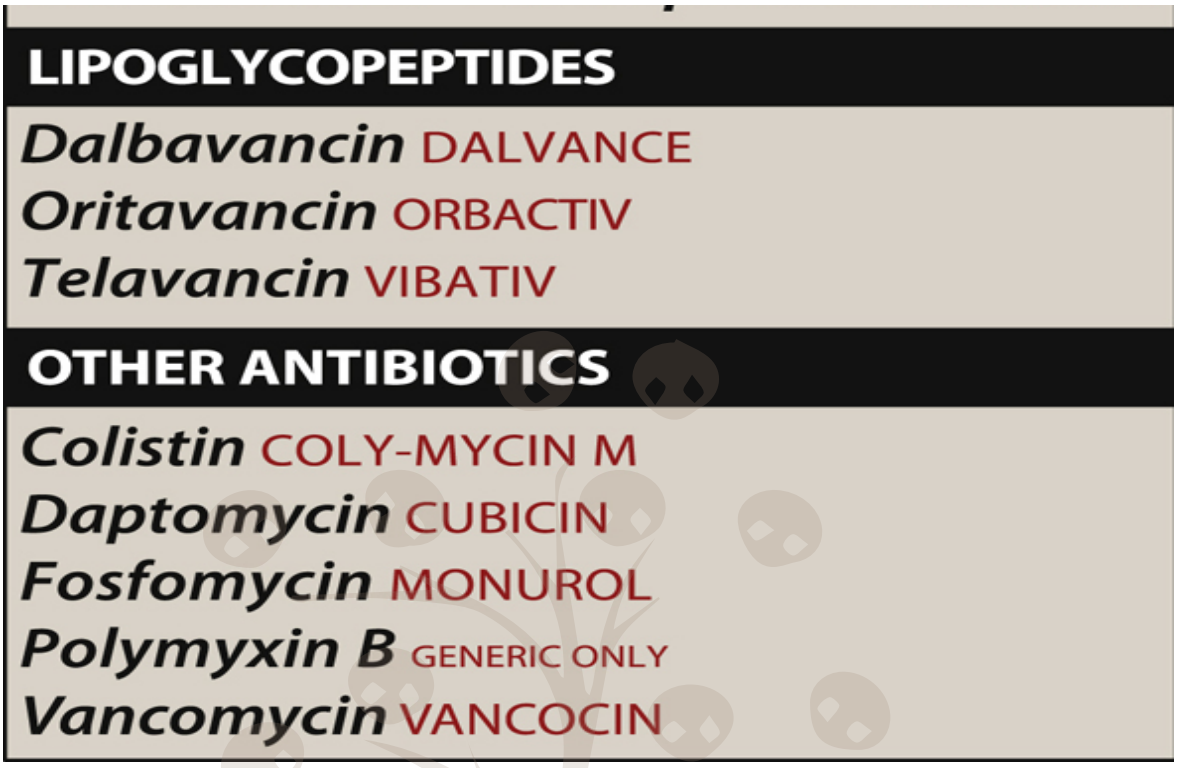

Figure 29.1 Summary of antimicrobial agents affecting cell wall synthesis.*Only available in oral formulation. **Available in oral and intravenous formulations.

II. PENICILLINS

The basic structure of penicillins consists of a core four-membered β-lactam ring, which is attached to a thiazolidine ring and an R side chain. Members of this family differ from one another in the R substituent attached to the 6-aminopenicillanic acid residue (Figure 29.2). The nature of this side chain affects the antimicrobial spectrum, stability to stomach acid, cross-hypersensitivity, and susceptibility to bacterial degradative enzymes (β-lactamases).

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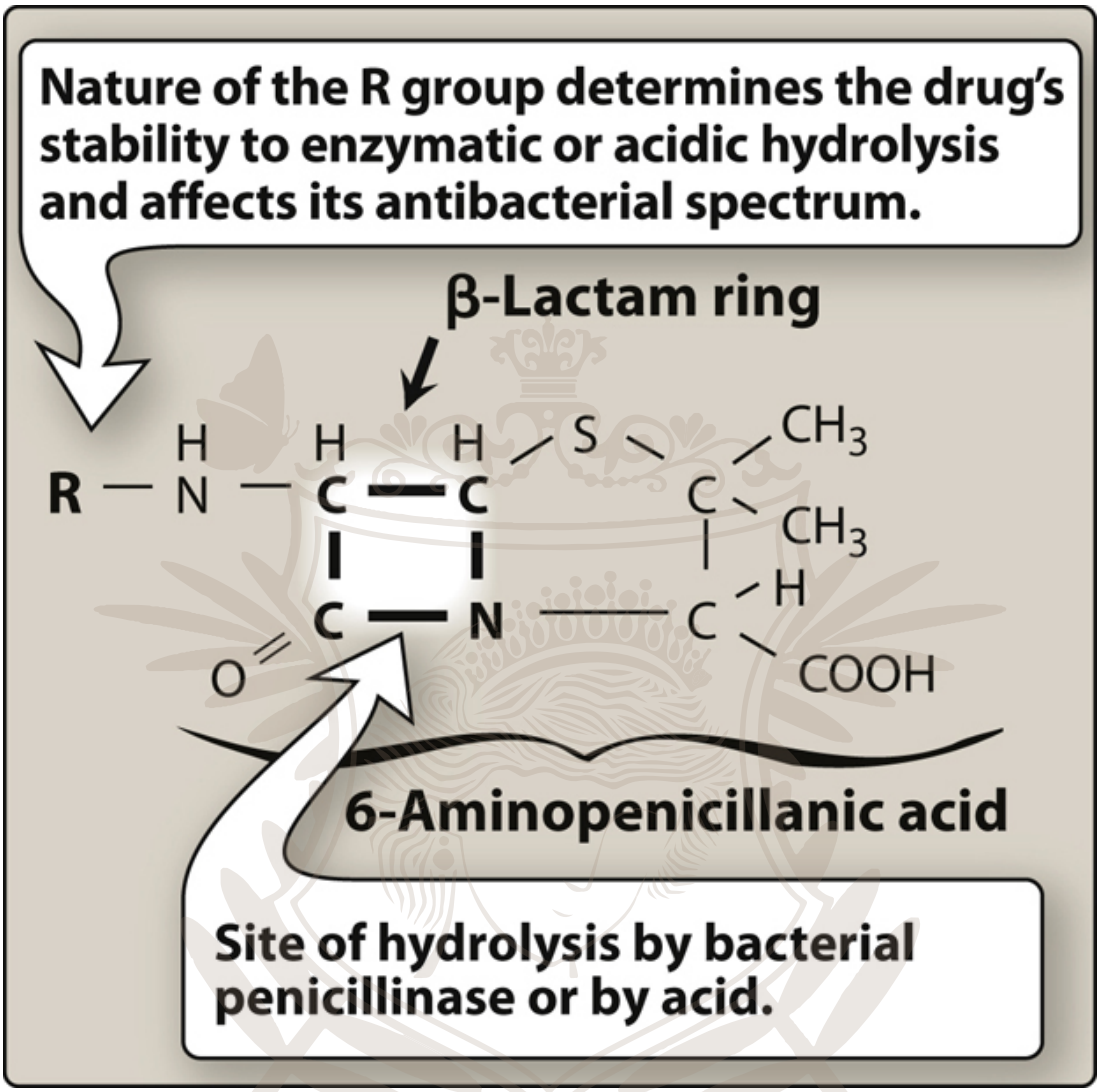

Figure 29.2 Structure of β-lactam antibiotics.

A. Mechanism of action

Penicillins interfere with the last step of bacterial cell wall synthesis, which is the cross-linking of adjacent peptidoglycan strands by a process known as transpeptidation. Since penicillins structurally resemble the terminal portion of the peptidoglycan strand, they compete for and bind to enzymes called penicillin-binding proteins (PBPs), which catalyze transpeptidase and facilitate cross-linking of the cell wall (Figure 29.3). The result is the formation of a weakened cell wall and ultimately cell death. For this reason, penicillins are regarded as bactericidal and work in a time-dependent fashion.

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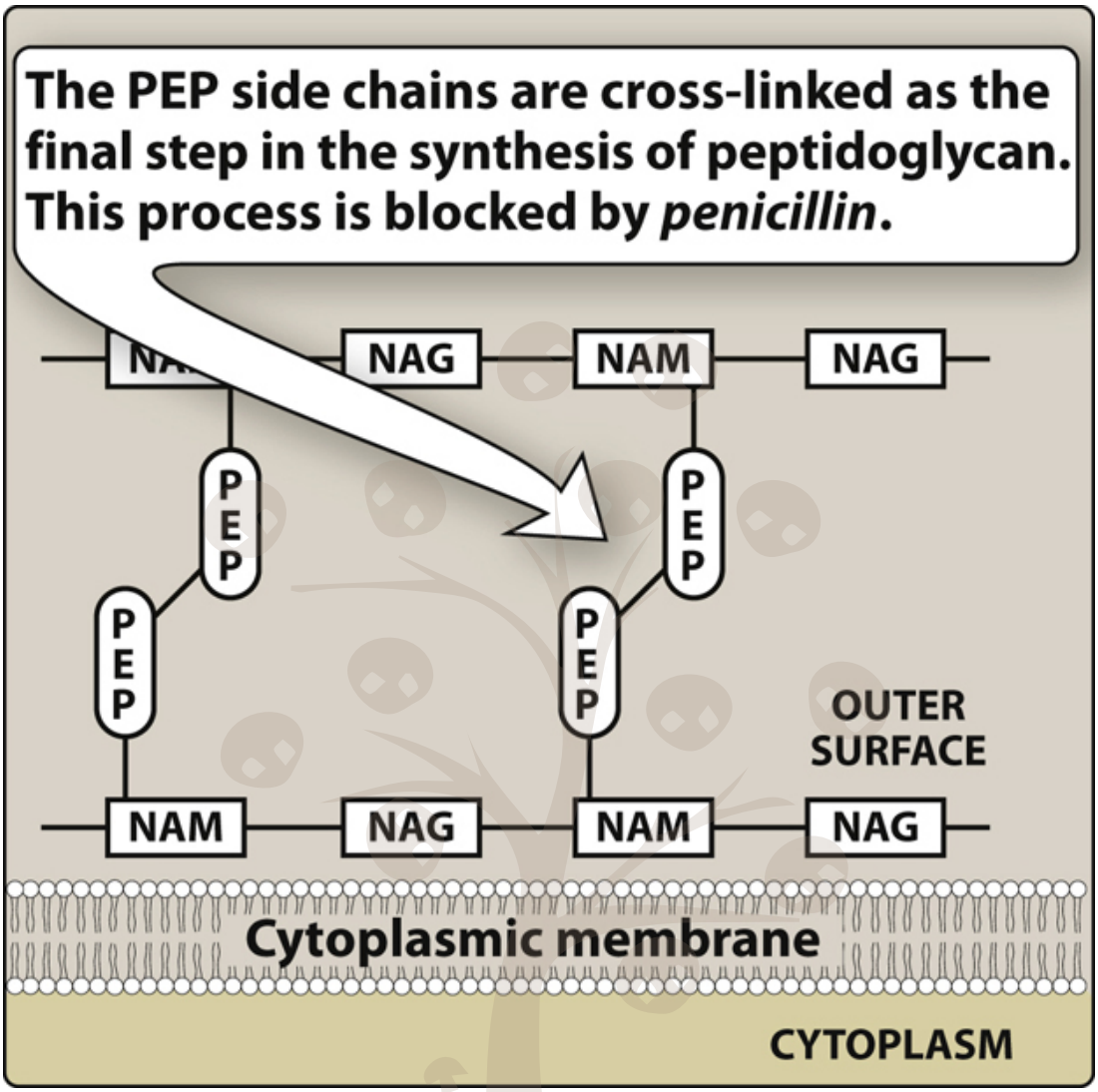

Figure 29.3 Bacterial cell wall of gram-positive bacteria.NAG = *N*-acetylglucosamine; NAM = *N*-acetylmuramic acid; PEP = cross-linking peptide.

B. Antibacterial spectrum

The antibacterial spectrum of the various penicillins is determined, in part, by their ability to cross the bacterial peptidoglycan cell wall to reach the PBPs in the periplasmic space. Factors determining PBP susceptibility to these antibiotics include size, charge, and hydrophobicity of the particular β-lactam antibiotic. In general, gram-positive microorganisms have cell walls that are easily traversed by penicillins, and, therefore, in the absence of resistance, they are susceptible to these drugs. Gram-negative microorganisms have an

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outer lipopolysaccharide membrane surrounding the cell wall that presents a barrier to the water-soluble penicillins. However, gram-negative bacteria have proteins inserted in the lipopolysaccharide layer that act as water-filled channels (called porins) to permit transmembrane entry.

1.Natural penicillins: *Penicillin G* and *penicillin V* are obtained from fermentations of the fungus Penicillium chrysogenum. *Penicillin* [pen-i-SILL-in] *G* (*benzylpenicillin*) has activity against a variety of gram-positive organisms, gram-negative organisms, and spirochetes (Figure 29.4). The potency of *penicillin G* is five to ten times greater than that of *penicillin V* against both Neisseria spp. and certain anaerobes. Most streptococci are very sensitive to *penicillin G*, but *penicillin*-resistant viridans streptococci and Streptococcus pneumoniae isolates are emerging. The vast majority of Staphylococcus aureus (greater than 90%) are now penicillinase producing and, therefore, resistant to *penicillin G.* Despite widespread use and increasing resistance in many types of bacteria, *penicillin* remains the drug of choice for the treatment of gas gangrene (Clostridium perfringens) and syphilis (Treponema pallidum). *Penicillin V*, only available in oral formulation, has a spectrum similar to that of *penicillin G*, but it is not used for treatment of severe infections because of its limited oral absorption. *Penicillin V* is more acid stable than is *penicillin G* and is the oral agent employed in the treatment of less severe infections.

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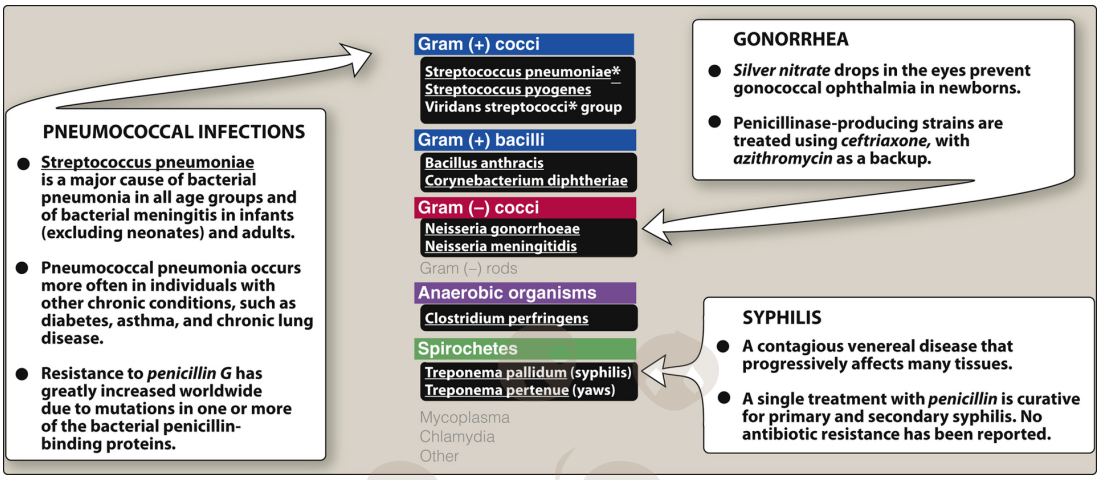

Figure 29.4 Typical therapeutic applications of *penicillin G*.*Resistant strains are increasingly seen.

2.Semisynthetic penicillins: *Ampicillin* [am-pi-SILL-in] and *amoxicillin* [a-mox-i-SILL-in] (also known as aminopenicillins or extended-spectrum penicillins) are created by chemical attachment of different R groups to the 6-aminopenicillanic acid nucleus. Addition of R groups extends the gram-negative antimicrobial activity of aminopenicillins to include Haemophilus influenzae, Escherichia coli, and Proteus mirabilis (Figure 29.5A). *Ampicillin* (with or without the addition of *gentamicin*) is the drug of choice for the gram-positive bacillus Listeria monocytogenes and susceptible enterococcal species. These extended-spectrum agents are also widely used in the treatment of respiratory infections, and *amoxicillin* is employed prophylactically by dentists in high-risk patients for the prevention of bacterial endocarditis. *Amoxicillin* and *ampicillin* are co-formulated with β-lactamase inhibitors, such as *clavulanic acid* or *sulbactam*, respectively, to combat infections caused by β-lactamase–producing organisms. For example, without the β-lactamase inhibitor, *methicillin*-sensitive Staphylococcus aureus (MSSA) is resistant to *ampicillin* and *amoxicillin.* Resistance in the form of plasmid-mediated penicillinases is a major clinical problem, which limits the use of aminopenicillins for some gram-negative organisms.

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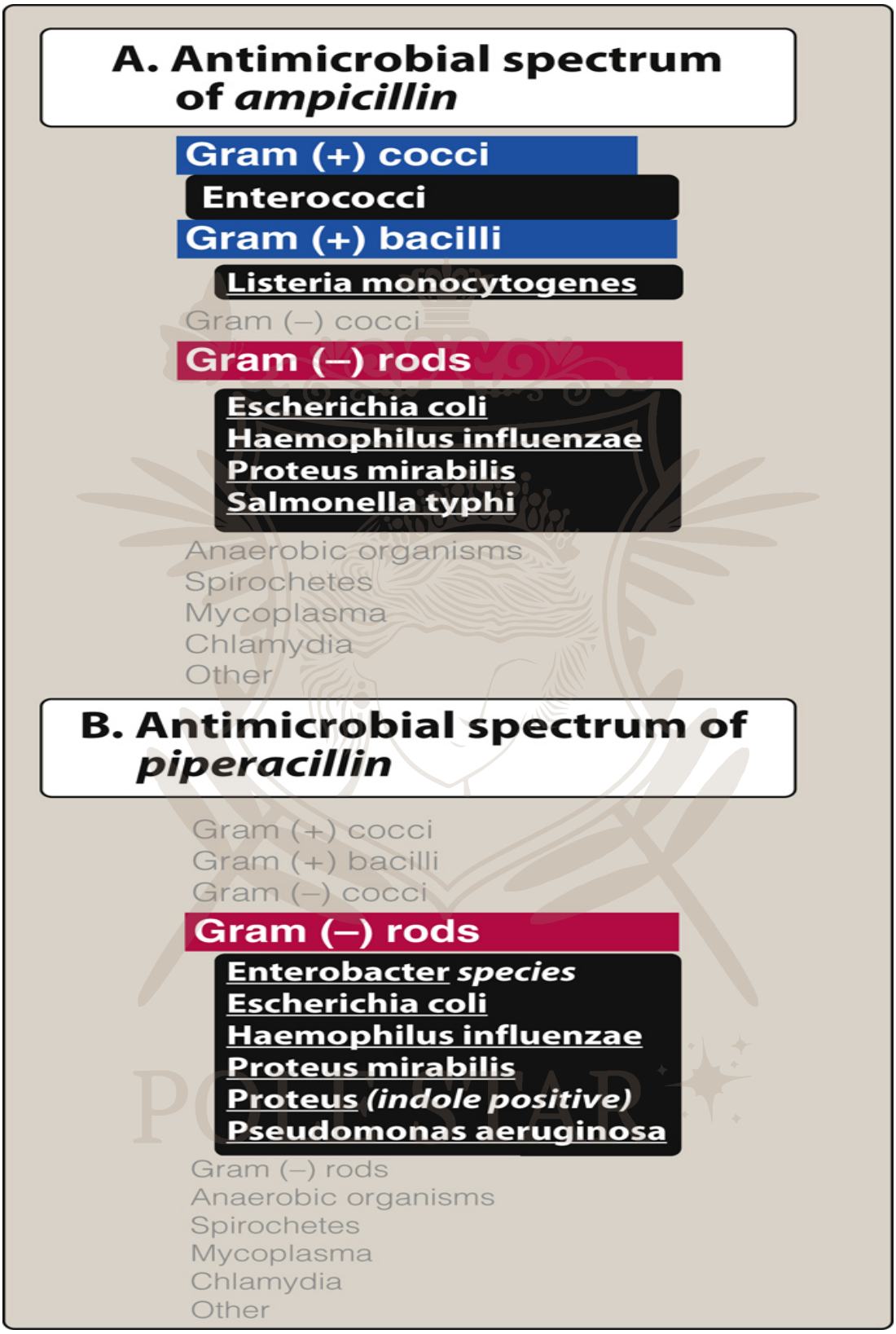

Figure 29.5 Antimicrobial activity of *ampicillin* (A) and *piperacillin* (B).

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3.Antistaphylococcal penicillins: *Methicillin* [meth-i-SILL-in], *nafcillin* [naf-SILL-in], *oxacillin* [ox-a-SILL-in], and *dicloxacillin* [dye-klox-a-SILL-in] are β-lactamase (penicillinase)-resistant penicillins. Their use is restricted to the treatment of infections caused by penicillinase-producing staphylococci, including MSSA. [Note: Because of its toxicity (interstitial nephritis), *methicillin* is not used clinically in the United States except in laboratory tests to identify resistant strains of S. aureus. *Methicillin*-resistant Staphylococcus aureus (MRSA) is currently a source of serious community and nosocomial (hospital-acquired) infections and is resistant to most commercially available β-lactam antibiotics.] The penicillinase-resistant penicillins have minimal-to-no activity against gram-negative infections.

4.Antipseudomonal penicillin: *Piperacillin* [pip-er-a-SILL-in] is also referred to as an antipseudomonal penicillin because of its activity against Pseudomonas aeruginosa (Figure 29.5B). Formulation of *piperacillin* with *tazobactam* extends the antimicrobial spectrum to include penicillinase-producing organisms (for example, most Enterobacterales and Bacteroides species). Figure 29.6 summarizes the stability of the penicillins to acid or the action of penicillinase.

Pharmacy Drug

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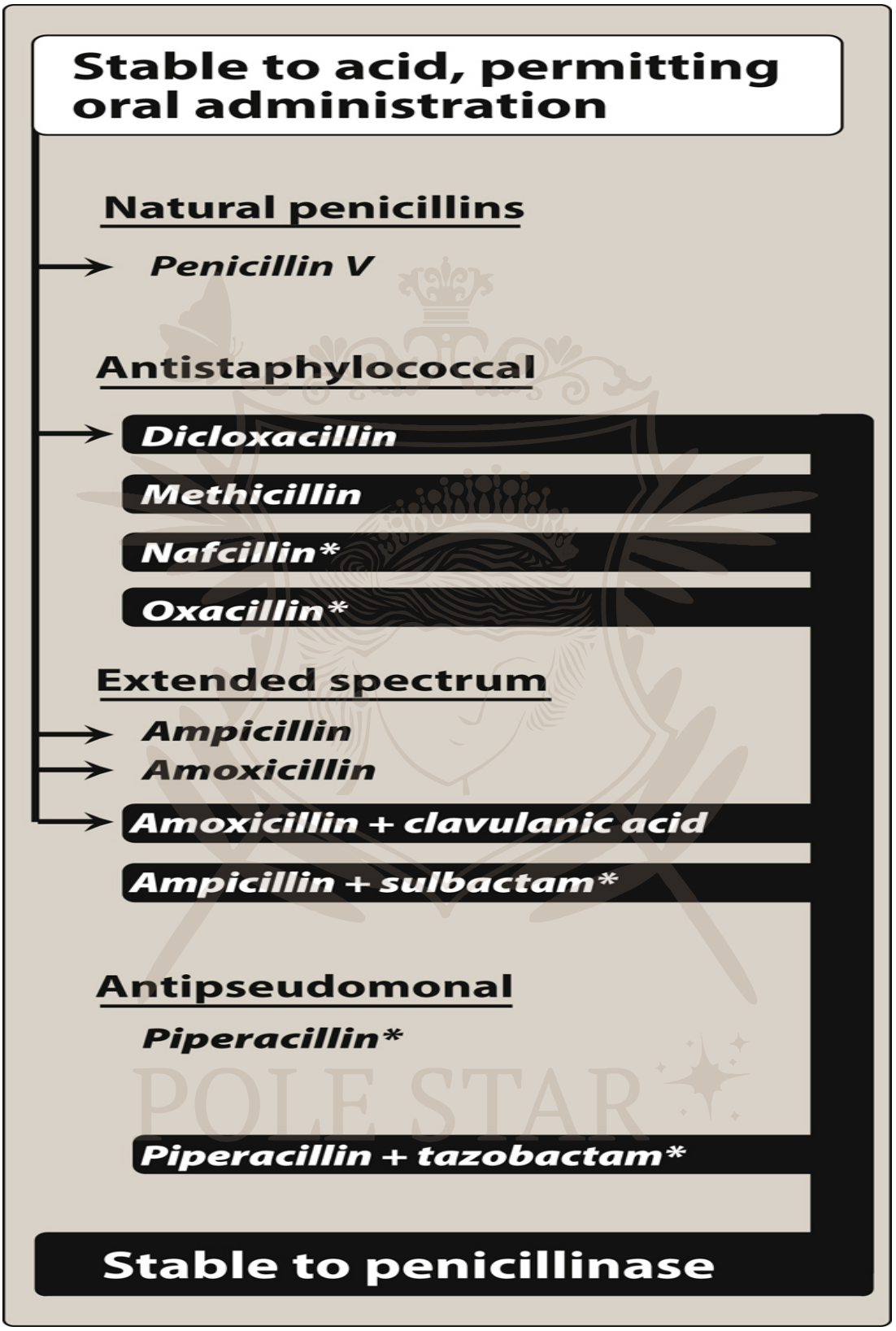
Stable to acid, permitting oral administration
Natural penicillins
Penicillin V
Antistaphylococcal
Dicloxacillin
Methicillin
Nafcillin*
Oxacillin*
Extended spectrum
Ampicillin
Amoxicillin
Amoxicillin + clavulanic acid
Ampicillin + sulbactam*
Antipseudomonal
Piperacillin*
Piperacillin + tazobactam*
Stable to penicillinase

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Figure 29.6 Stability of the penicillins to acid or the action of penicillinase. *Available only as parenteral preparation.

C. Resistance

Survival of bacteria in the presence of β-lactam antibiotics occurs due to the following:

1.β-Lactamase production: This family of enzymes hydrolyzes the cyclic amide bond of the β-lactam ring, which results in loss of bactericidal activity (Figure 29.2). They are the major cause of resistance to the penicillins and are an increasing clinical concern. β-Lactamases either are constitutive, mostly produced by the bacterial chromosome, or, more commonly, are acquired by the transfer of plasmids. Some of the β-lactam antibiotics are poor substrates for β-lactamases and resist hydrolysis, thus retaining activity against β-lactamase–producing organisms. [Note: Certain organisms may have chromosome-associated β-lactamases that are inducible by β-lactam antibiotics (for example, second- and third-generation cephalosporins).] Gram-positive organisms secrete β-lactamases extracellularly, whereas gram-negative bacteria inactivate β-lactam drugs in the periplasmic space.

2.Decreased permeability to the drug: Decreased penetration of the antibiotic through the outer cell membrane of the bacteria prevents the drug from reaching the target PBPs. In gram-positive bacteria, the peptidoglycan layer is near the surface of the bacteria and there are few barriers for the drug to reach its target. Reduced penetration of drug into the cell is a greater concern in gram-negative organisms, which have a complex cell wall that includes aqueous channels called porins. An excellent example of a pathogen lacking high permeability porins is P. aeruginosa. The presence of an efflux pump, which actively removes antibiotics from the site of action, can also reduce the amount of intracellular drug (for example, Klebsiella pneumoniae).

3.Altered PBPs: PBPs are bacterial enzymes involved in the synthesis of the cell wall and in the maintenance of morphologic

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features of the bacterium. β-Lactam antibiotics bind to PBPs and can prevent cell wall synthesis and lead to morphologic changes or lysis of susceptible bacteria. The number of PBPs varies with the type of organism. Modified PBPs have a lower affinity for β-lactam antibiotics, requiring clinically unattainable concentrations of the drug to effect inhibition of bacterial growth. MRSA occurs due to the presence of the mecA gene in S. aureus which produces modifications in the PBP, rendering the organism resistant to most commercially available β-lactams.

Clinical Application 29.1: Mechanisms of Resistance and Drug Selection

Extensive healthcare contact and prior antibiotic exposure place patients at risk for development of infection with multidrug-resistant organisms. Common gram-negative organisms associated with multidrug resistance in healthcare settings include P. aeruginosa, Klebsiella species, Acinetobacter species, and E. coli. Some infectious processes that may be caused by these organisms include bloodstream infections, pneumonia, and wound infections. Mechanisms of resistance that may reduce or eliminate activity of β-lactam antibiotics include enzymes that inactivate β-lactams through hydrolysis (that is, β-lactamases), change in PBP target sites, efflux pumps that move β-lactams out of the bacterial cell, and porin mutations that result in inability of β-lactams to enter the bacterial cell and reach their target site. Clinicians must consider potential mechanisms of resistance and the site of infection when selecting antibiotics to treat multidrug-resistant gram-negative infections.

D. Pharmacokinetics

1.Administration: The route of administration of a β-lactam antibiotic is determined by the stability of the drug to gastric acid and by the severity of the infection. The combination of *ampicillin* with *sulbactam*, *piperacillin* with *tazobactam*, and the antistaphylococcal penicillins *nafcillin* and *oxacillin* must be administered intravenously (IV) or intramuscularly (IM). *Penicillin V*, *amoxicillin*, and *dicloxacillin* are available only as oral preparations (Figure 29.6). [Note: The combination of *amoxicillin* with *clavulanic acid* is only available in an oral formulation in the United States.] *Procaine penicillin G* and *benzathine penicillin G* are administered IM and serve as depot forms. They are slowly

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absorbed into the circulation and persist at low levels over a long time period.

2.Absorption: The acidic environment within the intestinal tract is unfavorable for the absorption of penicillins. In the case of *penicillin V*, only one-third of an oral dose is absorbed under the best of conditions. Food decreases the absorption of the penicillinase-resistant penicillin *dicloxacillin* because as gastric emptying time increases, the drug is destroyed by stomach acid. Therefore, it should be taken on an empty stomach. Conversely, *amoxicillin* is stable in acid and is readily absorbed from the gastrointestinal tract.

3.Distribution: The β-lactam antibiotics distribute well throughout the body. All the penicillins cross the placental barrier, but none have been shown to have teratogenic effects. However, penetration into bone or cerebrospinal fluid (CSF) is insufficient for therapy unless these sites are inflamed (Figures 29.7 and 29.8). [Note: Inflamed meninges are more permeable to the penicillins, resulting in an increased ratio of the drug in the CSF compared to the serum.] *Penicillin* levels in the prostate are insufficient to be effective against infections.

Pharmacy Drug

A L G r a w a n y

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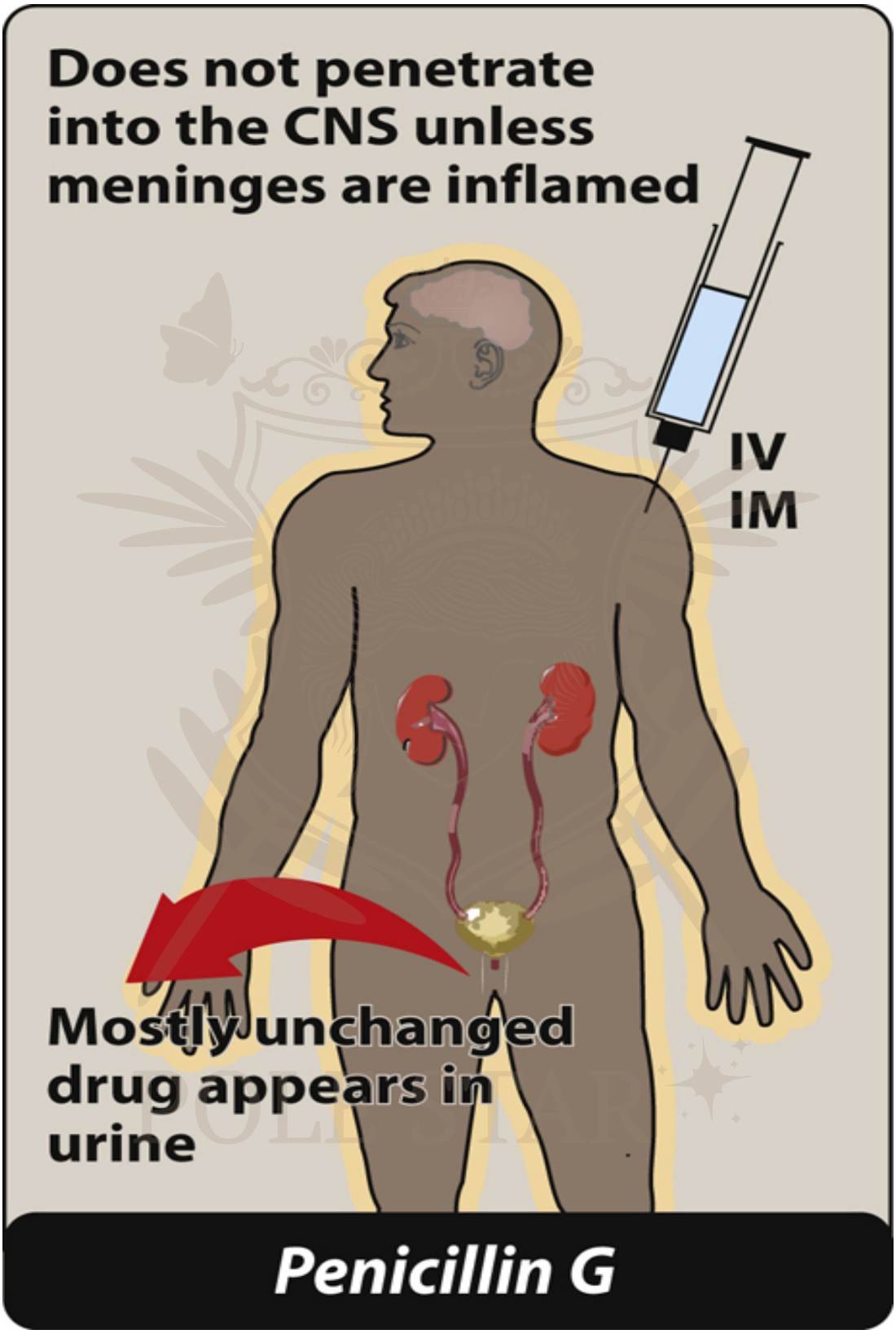
Does not penetrate into the CNS unless meninges are inflamed
IV
IM
Mostly unchanged drug appears in urine
Penicillin G

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Figure 29.7 Administration and fate of *penicillin*.CNS = central nervous system.

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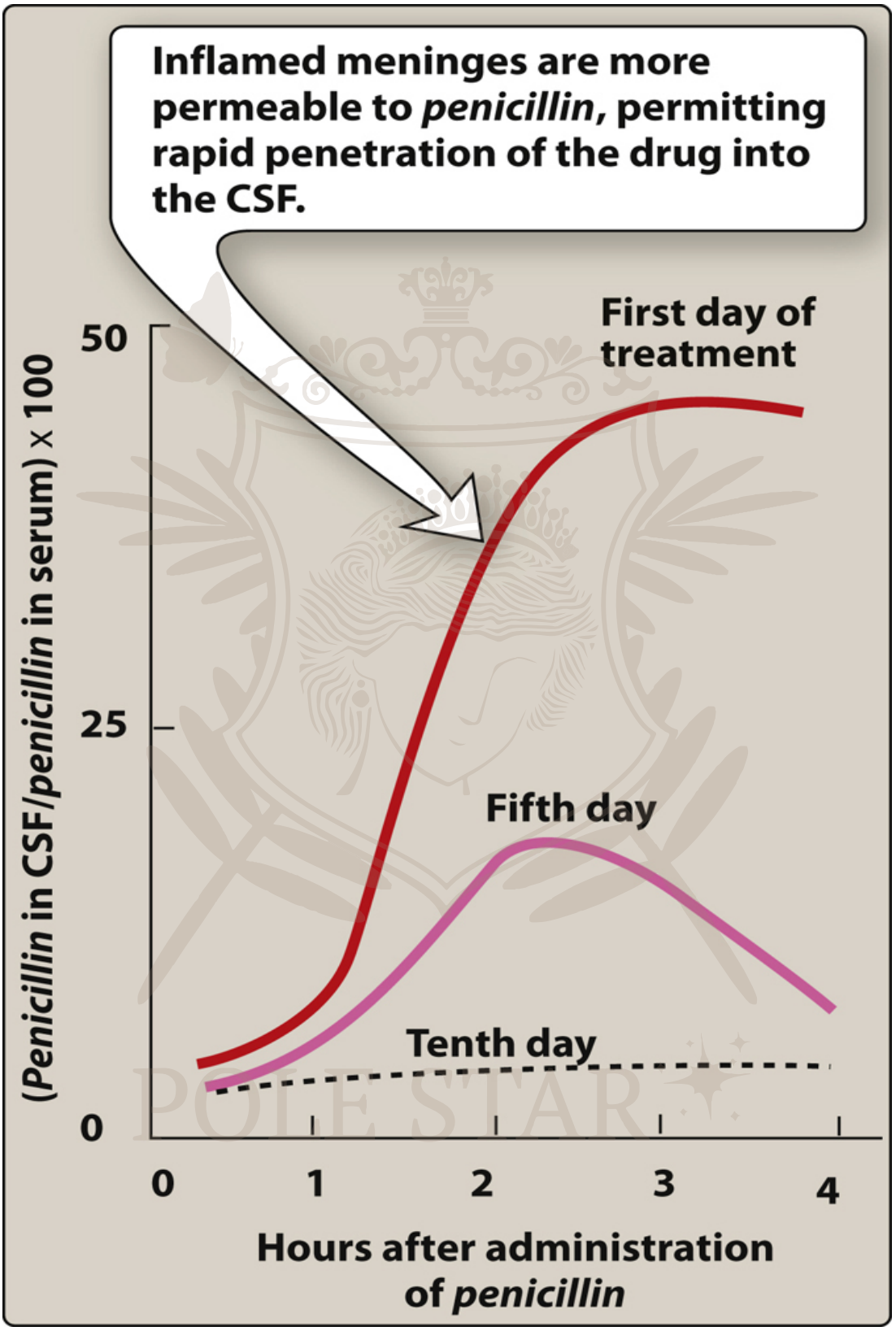
Inflamed meninges are more permeable to *penicillin*, permitting rapid penetration of the drug into the CSF.
First day of treatment
Fifth day
Tenth day
(*Penicillin* in CSF/*penicillin* in serum) × 100
50
25
0
0
1
2
3
4
Hours after administration of *penicillin*

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Figure 29.8 Enhanced penetration of *penicillin* into the cerebral spinal fluid (CSF) during inflammation.

4.Metabolism: Host metabolism of the β-lactam antibiotics is usually insignificant, but some metabolism of *penicillin G* may occur in patients with impaired renal function. *Nafcillin* and *oxacillin* are exceptions to the rule and are primarily metabolized in the liver.

5.Excretion: The primary route of excretion is through the organic acid (tubular) secretory system of the kidney as well as by glomerular filtration. Patients with impaired renal function must have dosage regimens adjusted. Because *nafcillin* and *oxacillin* are primarily metabolized in the liver, they do not require dose adjustment in renal insufficiency. *Probenecid* inhibits the secretion of penicillins by competing for active tubular secretion via the organic acid transporter and, thus, can increase blood levels. The penicillins are also excreted in breast milk.

E. Adverse reactions

Penicillins are among the safest drugs. However, adverse reactions may occur (Figure 29.9).

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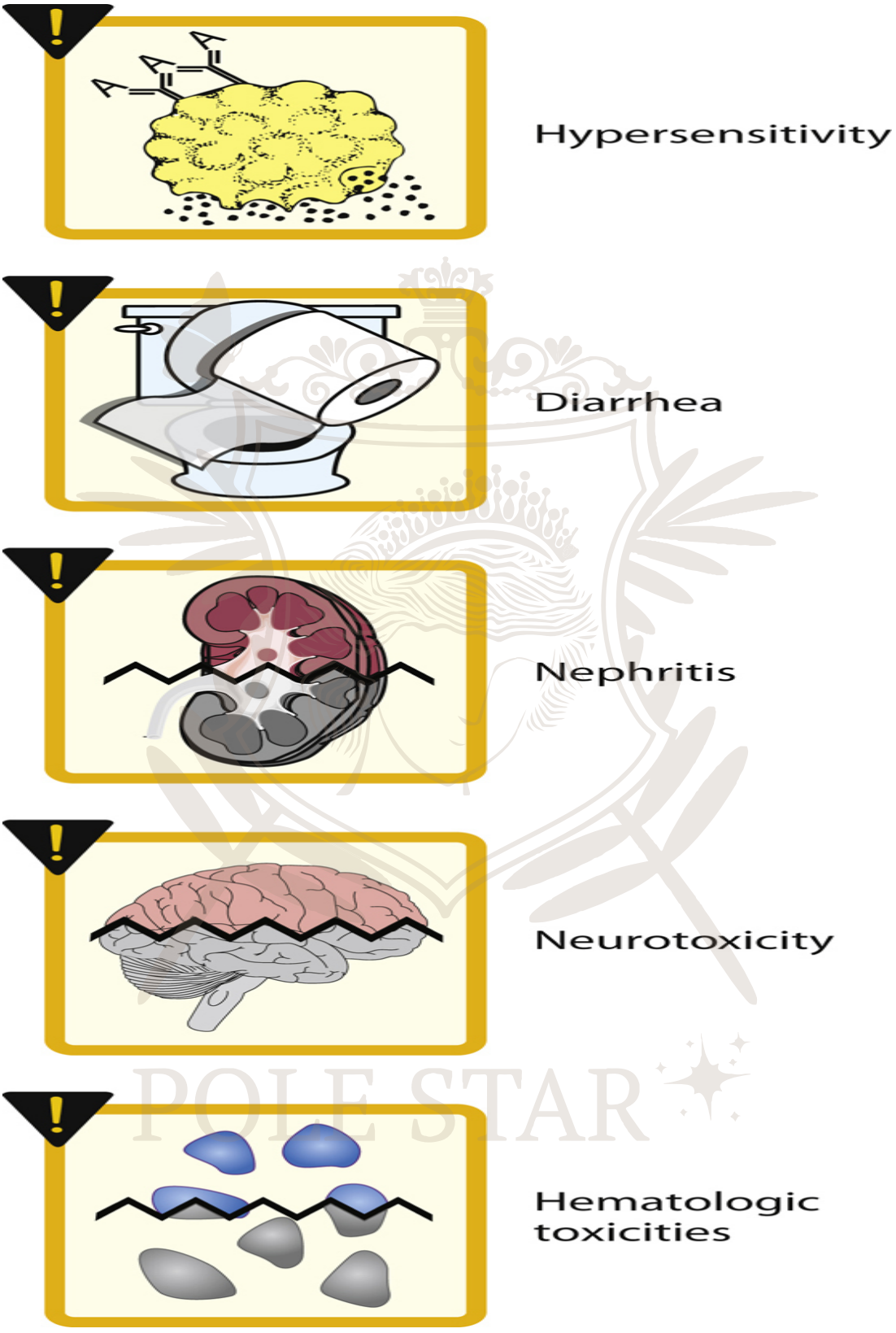

Figure 29.9 Summary of the adverse effects of penicillins.

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1.Hypersensitivity: Approximately 10% of patients self-report allergy to penicillins. Of these, 90% do not have a true Type 1, IgE-mediated hypersensitivity reaction. Allergic reactions range from rashes to angioedema (marked swelling of the lips, tongue, and periorbital area) and anaphylaxis. In patients with allergy to penicillins, cross-reactivity may occur with other β-lactam antibiotics. To determine whether treatment with a β-lactam is safe when an allergy is noted, patient history regarding severity of previous reaction is essential.

2.Diarrhea: Diarrhea is a common problem that is caused by a disruption of the normal balance of intestinal microorganisms. It occurs to a greater extent with those agents that are incompletely absorbed and have an extended antibacterial spectrum. Pseudomembranous colitis from Clostridioides difficile and other organisms may occur with penicillin use.

3.Nephritis: Penicillins, particularly *methicillin*, have the potential to cause acute interstitial nephritis. [Note: *Methicillin* is therefore no longer used clinically.]

4.Neurotoxicity: The penicillins are irritating to neuronal tissue, and they can provoke seizures if injected intrathecally or if very high blood levels are reached. Patients with epilepsy are particularly at risk due to the ability of penicillins to cause GABAergic inhibition.

5.Hematologic toxicities: Decreased coagulation may be observed with high doses of *piperacillin* and *nafcillin* (and, to some extent, with *penicillin G*). Cytopenias have been associated with therapy of greater than 2 weeks, and therefore, blood counts should be monitored weekly for such patients.

III. CEPHALOSPORINS

The cephalosporins are β-lactam antibiotics closely related both structurally and functionally to penicillins. Most cephalosporins are produced semisynthetically by the chemical attachment of side chains to

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7-aminocephalosporanic acid. Structural changes on the acyl side chain at the 7-position alter antibacterial activity, and variations at the 3-position modify the pharmacokinetic profile (Figure 29.10). Cephalosporins have the same mode of action as penicillins, and they are affected by the same resistance mechanisms. However, they tend to be more stable than the penicillins to certain β-lactamases.

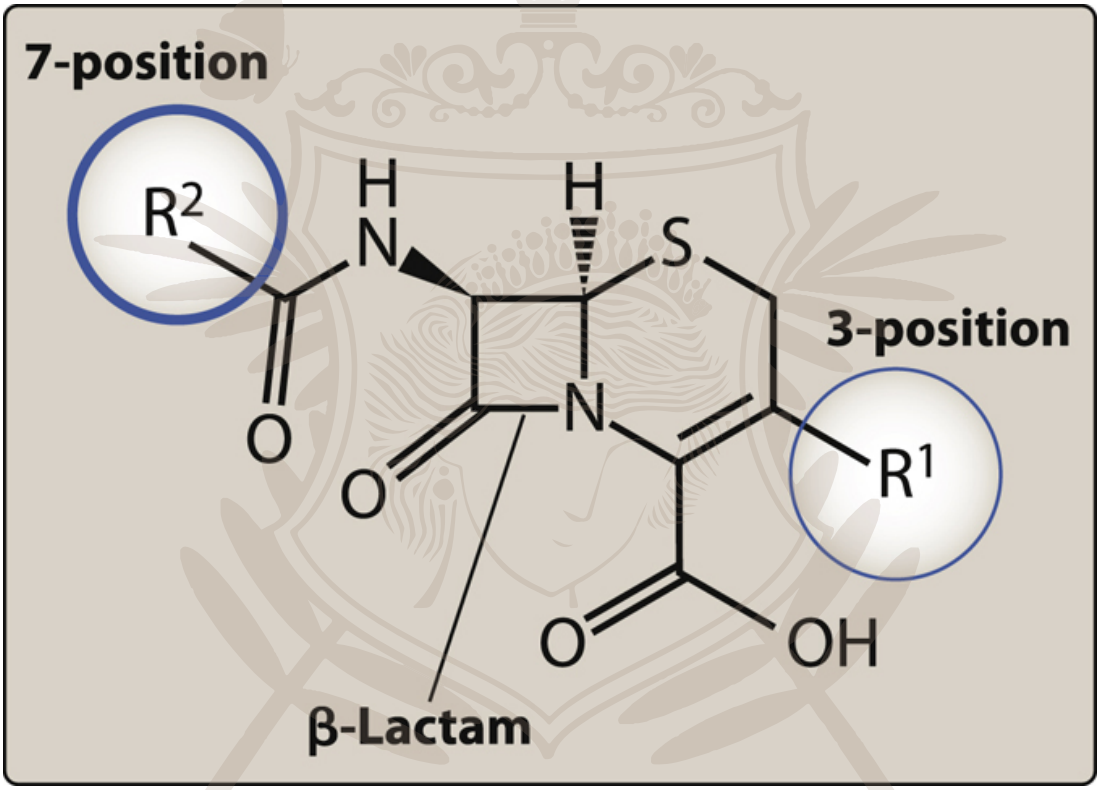

Figure 29.10 Structural features of cephalosporin antibiotics.

A. Antibacterial spectrum

Cephalosporins have been classified as first, second, third, fourth, and advanced generation, based largely on their bacterial susceptibility patterns and resistance to β-lactamases (Figure 29.11). [Note: Commercially available cephalosporins are ineffective against L. monocytogenes, C. difficile, and the enterococci.]

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First-generation cephalosporins

Gram (+) cocci

- Staphylococcus aureus*
- Staphylococcus epidermidis
- Streptococcus pneumoniae
- Streptococcus pyogenes
- Anaerobic streptococci

Gram (–) rods

- Escherichia coli
- Klebsiella pneumoniae
- Proteus mirabilis

Second-generation cephalosporins

Gram (+) cocci

- Staphylococcus aureus*
- Streptococcus pneumoniae
- Streptococcus pyogenes
- Anaerobic streptococci

Gram (–) cocci

- Neisseria gonorrhoeae

Gram (–) rods

- Enterobacter aerogenes
- Escherichia coli
- Haemophilus influenzae
- Klebsiella pneumoniae
- Proteus mirabilis

Anaerobic organisms**

Third-generation cephalosporins

Gram (+) cocci

- Streptococcus pneumoniae
- Streptococcus pyogenes
- Anaerobic streptococci

Gram (–) cocci

- Neisseria gonorrhoeae

Gram (–) rods

- Enterobacter aerogenes
- Escherichia coli
- Haemophilus influenzae
- Klebsiella pneumoniae
- Proteus mirabilis
- Pseudomonas aeruginosa†
- Serratia marcescens

Fourth-generation cephalosporins

Antibacterial coverage comparable to that of the third-generation class; however, demonstrate greater stability against β-lactamases

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Figure 29.11 Summary of therapeutic applications of cephalosporins.* *Methicillin*-resistant staphylococci are resistant. ** *Cefoxitin* and *cefotetan* have anaerobic coverage. † *Ceftazidime* only.

1.First generation: The first-generation cephalosporins act as *penicillin G* substitutes. They are resistant to the staphylococcal penicillinase (that is, they cover MSSA). Isolates of S. pneumoniae resistant to *penicillin* are also resistant to first-generation cephalosporins. Agents in this generation also have modest activity against P. mirabilis, E. coli, and K. pneumoniae. Most oral cavity anaerobes like Peptostreptococcus are sensitive, but the *Bacteroides fragilis* group is resistant.

2.Second generation: The second-generation cephalosporins display greater activity against gram-negative organisms, such as H. influenzae, Klebsiella species, Proteus species, E. coli, and Moraxella catarrhalis, whereas activity against gram-positive organisms is weaker. Antimicrobial coverage of the cephamycins (*cefotetan* [sef-oh-TEE-tan] and *cefoxitin* [sef-OX-i-tin]) also includes anaerobes (for example, B. fragilis). They are the only cephalosporins commercially available with appreciable activity against gram-negative anaerobic bacteria. However, neither drug is first line because of the increasing prevalence of resistance among *B. fragilis*.

3.Third generation: These cephalosporins have assumed an important role in the treatment of infectious diseases. Although they are less potent than first-generation cephalosporins against MSSA, the third-generation cephalosporins have enhanced activity against gram-negative bacilli, including β-lactamase producing strains of H. influenzae and Neisseria gonorrhoeae. The spectrum of activity of this class includes enteric organisms, such as Serratia marcescens and Providencia species. *Ceftriaxone* [sef-trye-AKS-own] and *cefotaxime* [sef-oh-TAKS-eem] have become agents of choice in the treatment of meningitis. *Ceftazidime* [sef-TA-zi-deem] has activity against P. aeruginosa; however, resistance is increasing and use should be evaluated on a case-by-case basis.

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Third-generation cephalosporins must be used with caution, as they are associated with significant “collateral damage,” including the induction of antimicrobial resistance and development of C. difficile infection. [Note: Fluoroquinolone use is also associated with collateral damage.]

4.Fourth generation: *Cefepime* [SEF-eh-peem] is classified as a fourth-generation cephalosporin and must be administered parenterally. *Cefepime* has a wide antibacterial spectrum, with activity against streptococci and staphylococci (but only those that are *methicillin* susceptible). *Cefepime* is also effective against aerobic gram-negative organisms, such as *Enterobacter* species, E. coli, K. pneumoniae, P. mirabilis, and P. aeruginosa. When selecting an antibiotic that is active against P. aeruginosa, clinicians should refer to the local antibiogram (laboratory testing for the sensitivity of an isolated bacterial strain to different antibiotics) for direction.

5.Advanced generation: *Ceftaroline* [sef-TAR-oh-leen] is a broad-spectrum, advanced-generation cephalosporin. It is the only β-lactam in the United States with activity against MRSA, and it is indicated for the treatment of complicated skin and skin structure infections and community-acquired pneumonia. The unique structure allows *ceftaroline* to bind to PBPs found in MRSA and penicillin-resistant S. pneumoniae. In addition to its broad gram-positive activity, it also has gram-negative activity similar to the third-generation cephalosporin *ceftriaxone.* Important gaps in coverage include P. aeruginosa, extended-spectrum β-lactamase (ESBL)–producing Enterobacterales, and Acinetobacter baumannii. The twice-daily dosing regimen also limits use outside of an institutional setting.

Cefiderocol [sef-i-DER-oh-kol] is an advanced-generation cephalosporin with activity against aerobic gram-negative organisms, including those that are multidrug resistant. It has no activity against gram-positive organisms. *Cefiderocol* is approved for the treatment of complicated urinary tract infections, including pyelonephritis, and hospital-acquired and ventilator-associated pneumonia. The drug possesses a novel mechanism of action

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utilizing iron. *Cefiderocol* acts as a siderophore to bind to extracellular free ferric iron and enters into the bacterial cell membrane through both passive diffusion and active transport via the iron uptake mechanism. It is one of the few antibacterials with dose adjustment recommended for patients with augmented renal clearance (for example, four times daily dosing). Due to its unique mechanism, it remains active against multidrug-resistant gram-negative bacteria which produce many β-lactamases such as Klebsiella pneumoniae carbapenemase (KPC), OXA-type β-lactamase, and metallo-β-lactamase (MBL).

B. Resistance

Resistance to the cephalosporins is either due to the hydrolysis of the β-lactam ring by β-lactamases or reduced affinity for PBPs.

C. Pharmacokinetics

1.Administration: Many of the cephalosporins must be administered IV or IM (Figure 29.12) because of their poor oral absorption. Exceptions are noted in Figure 29.13.

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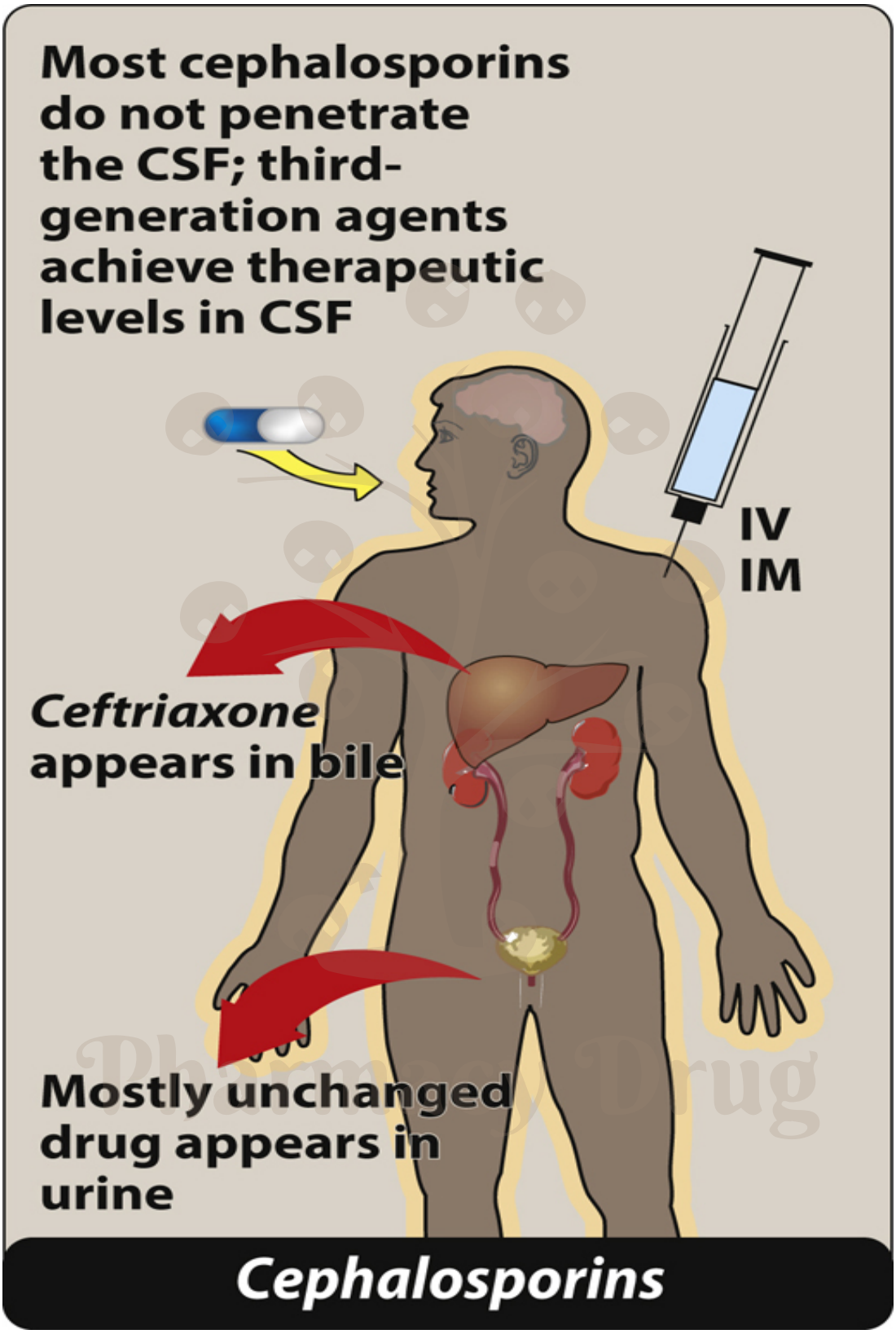

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Figure 29.12 Administration and fate of the cephalosporins.CSF = cerebrospinal fluid.

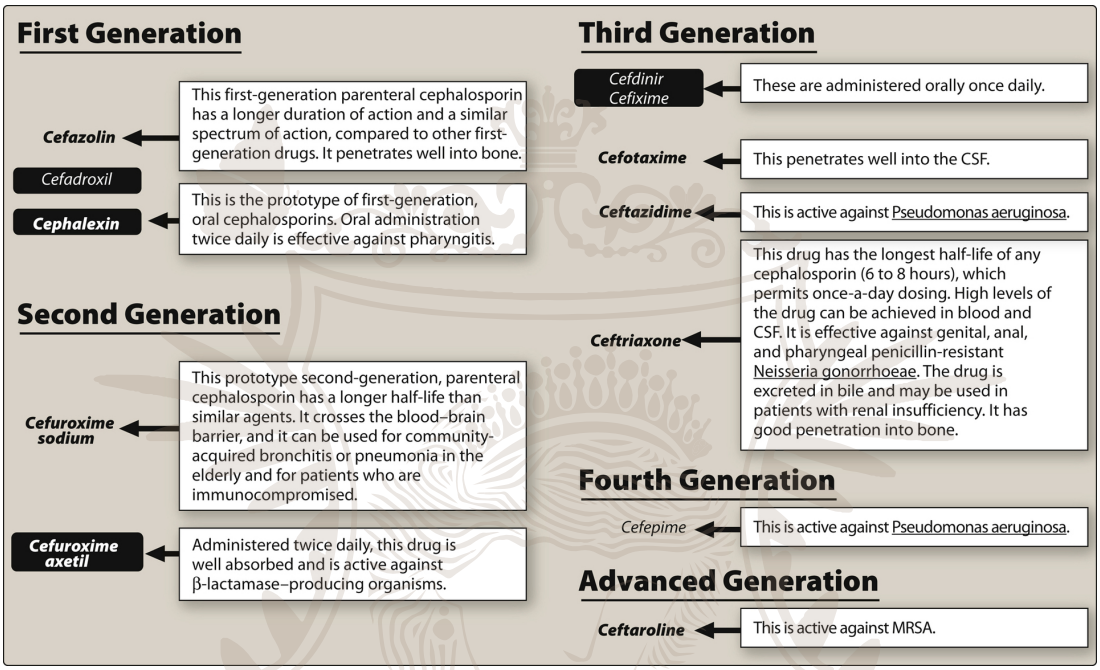

Figure 29.13 Therapeutic advantages of some clinically useful cephalosporins.[Note: Drugs that can be administered orally are shown in reverse type. More useful drugs shown in bold.]. CSF = cerebrospinal fluid; MRSA = *methicillin*-resistant Staphylococcus aureus.

2.Distribution: All cephalosporins distribute very well into body fluids. However, adequate therapeutic levels in the CSF, regardless of inflammation, are achieved with only a few cephalosporins. For example, *ceftriaxone* and *cefotaxime* are effective in the treatment of neonatal and childhood meningitis caused by H. influenzae. *Cefazolin* [se-FA-zo-lin] is commonly used for surgical prophylaxis due to its activity against penicillinase-producing S. aureus, along with its good tissue and fluid penetration.

3.Elimination: Cephalosporins are eliminated through tubular secretion and/or glomerular filtration (Figure 29.12). Therefore,

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doses must be adjusted in renal dysfunction to guard against accumulation and toxicity. One exception is *ceftriaxone*, which is excreted through the bile into the feces and, therefore, is frequently employed in patients with renal insufficiency.

D. Adverse effects

Like the penicillins, the cephalosporins are generally well tolerated. However, allergic reactions are a concern. Patients who have had an anaphylactic response, Stevens-Johnson syndrome, or toxic epidermal necrolysis to penicillins should not receive cephalosporins. Cephalosporins should be avoided or used with caution in individuals with penicillin allergy. Current data suggest that the cross-reactivity between penicillin and cephalosporins is around 3% to 5% and is determined by the similarity in the side chain, not the β-lactam structure. The highest rate of allergic cross-sensitivity is between *penicillin* and first-generation cephalosporins.

Clinical Application 29.2: Considerations for Administration of β-Lactam Antibiotics

β-Lactam antibiotics, which include penicillins, cephalosporins, monobactams, and carbapenems, are considered to be time-dependent agents. This means that bacterial killing is maximized when drug concentrations are above the minimum inhibitory concentration (MIC) of the pathogen for a greater percent of each dosing interval. The MIC of a pathogen is the minimum concentration of an antibiotic that prevents visible growth of bacteria. This information about the activity of β-lactams can be utilized to optimize how these antibiotics are dosed in the clinical setting. For example, most intravenous β-lactam antibiotics are infused over a period of 30 minutes to 1 hour. However, by extending infusions (over 3 or 4 hours), the β-lactam can more effectively eliminate bacteria, since drug concentrations are likely to be above the MIC for a greater time. β-Lactams can also be administered over 24 hours. This is referred to as a continuous infusion. The stability of the antibiotic should be carefully considered prior to utilizing an extended or continuous infusion strategy.

IV. OTHER B-LACTAM ANTIBIOTICS

A. Carbapenems

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Carbapenems are synthetic β-lactam antibiotics that differ in structure from the penicillins in that the sulfur atom of the thiazolidine ring (Figure 29.2) has been externalized and replaced by a carbon atom (Figure 29.14). *Imipenem* [i-mi-PEN-em], *meropenem* [mer-oh-PEN-em], *doripenem* [dore-i-PEN-em], and *ertapenem* [er-ta-PEN-em] are drugs in this group.

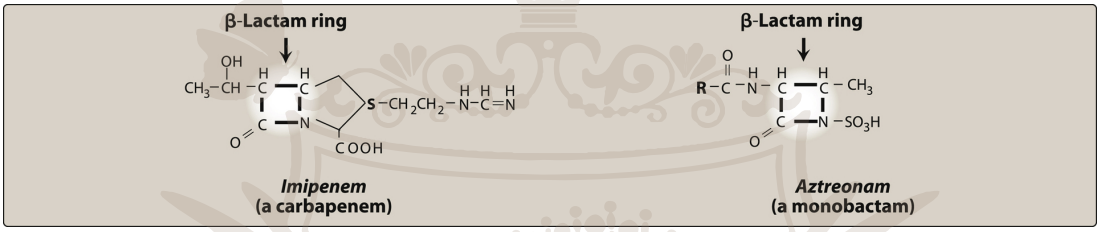

Figure 29.14 Structural features of *imipenem* and *aztreonam*.

1.Antibacterial spectrum: *Imipenem* resists hydrolysis by most β-lactamases, but not the MBLs. This drug plays a role in empiric therapy because it is active against β-lactamase–producing gram-positive and gram-negative organisms, anaerobes, and P. aeruginosa (Figure 29.15). *Meropenem* and *doripenem* have antibacterial activity similar to that of *imipenem. Doripenem* may retain activity against resistant isolates of Pseudomonas. Unlike other carbapenems, *ertapenem* lacks coverage against P. aeruginosa, Enterococcus species, and Acinetobacter species.

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Gram (+) cocci

- Staphylococcus aureus*
- Staphylococcus epidermidis
- Enterococcus faecalis
- Streptococcus groups A, B, C
- Streptococcus pneumoniae

Gram (+) bacilli

- Listeria monocytogenes

Gram (–) cocci

- Neisseria gonorrhoeae**
- Neisseria meningitidis

Gram (–) rods

- Acinetobacter species
- Citrobacter species
- Enterobacter species
- Escherichia coli
- Gardnerella vaginalis
- Haemophilus influenzae
- Klebsiella species
- Proteus species
- Providencia species
- Pseudomonas aeruginosa
- Salmonella species
- Serratia species

Anaerobic organisms

- Clostridium species
- Peptococcus species
- Peptostreptococcus species
- Cutibacterium species
- Bacteroides species
- Fusobacterium species

Spirochetes
Mycoplasma
Chlamydia

Other

- Actinomyces
- Nocardia species

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Figure 29.15 Antimicrobial spectrum of *imipenem*.* *Methicillin*-resistant staphylococci are resistant. **Includes penicillinase-producing strains.

2.Pharmacokinetics: *Imipenem*, *meropenem*, and *doripenem* are administered IV and penetrate well into body tissues and fluids, including the CSF when the meninges are inflamed. *Meropenem* is known to reach therapeutic levels in bacterial meningitis even without inflammation. These agents are excreted by glomerular filtration. *Imipenem* undergoes cleavage by a dehydropeptidase found in the brush border of the proximal renal tubule. Compounding *imipenem* with *cilastatin* protects the parent drug from renal dehydropeptidase and, thus, prolongs its activity in the body. The other carbapenems do not require coadministration of *cilastatin. Ertapenem* is administered IV once daily. [Note: Doses of these agents must be adjusted in patients with renal insufficiency.]

3.Adverse effects: *Imipenem*/*cilastatin* can cause nausea, vomiting, and diarrhea. Eosinophilia and neutropenia are less common than with other β-lactams. High levels of *imipenem* may provoke seizures; however, the other carbapenems are less likely to do so. Carbapenems and *penicillin* share a common bicyclic core. Structural similarity may confer cross-reactivity between classes. While those with true *penicillin* allergy should use carbapenems cautiously, the cross-reactivity rate seen in studies is very low (less than 1%).

B. Monobactams

The monobactams, which also disrupt bacterial cell wall synthesis, are unique because the β-lactam ring is not fused to another ring (Figure 29.14). *Aztreonam* [az-TREE-oh-nam], which is the only commercially available monobactam, has antimicrobial activity directed primarily against gram-negative pathogens, including the Enterobacterales and P. aeruginosa. It lacks activity against gram-positive organisms and anaerobes. *Aztreonam* is administered either IV or IM and can accumulate in patients with renal failure. *Aztreonam* is relatively nontoxic, but it may cause phlebitis, skin rash, and, occasionally,

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abnormal liver function tests. This drug has a low immunogenic potential, and it shows little cross-reactivity with antibodies induced by other β-lactams. Thus, this drug may offer a safe alternative for treating patients who are allergic to other penicillins, cephalosporins, or carbapenems. One notable exception is the potential for cross-reactivity of *aztreonam* in patients with allergy to *ceftazidime*, due similarity of a side chain in both structures.

V. B-LACTAMASE INHIBITORS

Hydrolysis of the β-lactam ring, either by enzymatic cleavage with a β-lactamase or by acid, destroys the antimicrobial activity of a β-lactam antibiotic. There are a growing number of β-lactamases, with over 4,000 types reported. These enzymes are classified based on the structure and hydrolytic pattern. The simplest classification method categorizes β-lactamases into four classes (A to D) based on protein sequences.

β-Lactamase inhibitors, such as *clavulanic* [cla-vue-LAN-ick] *acid*, *sulbactam* [sul-BAK-tam], and *tazobactam* [ta-zoh-BAK-tam], contain a β-lactam ring but, by themselves, do not have significant antibacterial activity or cause any significant adverse effects. *Avibactam* [av-ee-BACK-tam], *vaborbactam* [vay-bor-BACK-tam], and *relebactam* [re-le-BAK-tam] are also β-lactamase inhibitors; however, their structures lack the core β-lactam ring. β-Lactamase inhibitors function by inactivating β-lactamases, thereby protecting the antibiotics that are normally substrates for these enzymes. The β-lactamase inhibitors are, therefore, formulated in combination with β-lactamase–sensitive antibiotics, such as *amoxicillin*, *ampicillin*, and *piperacillin* (Figure 29.1). Figure 29.16 shows the effect of *clavulanic acid* and *amoxicillin* on the growth of β-lactamase–producing E. coli. [Note: *Clavulanic acid* is nearly devoid of any antibacterial activity.]

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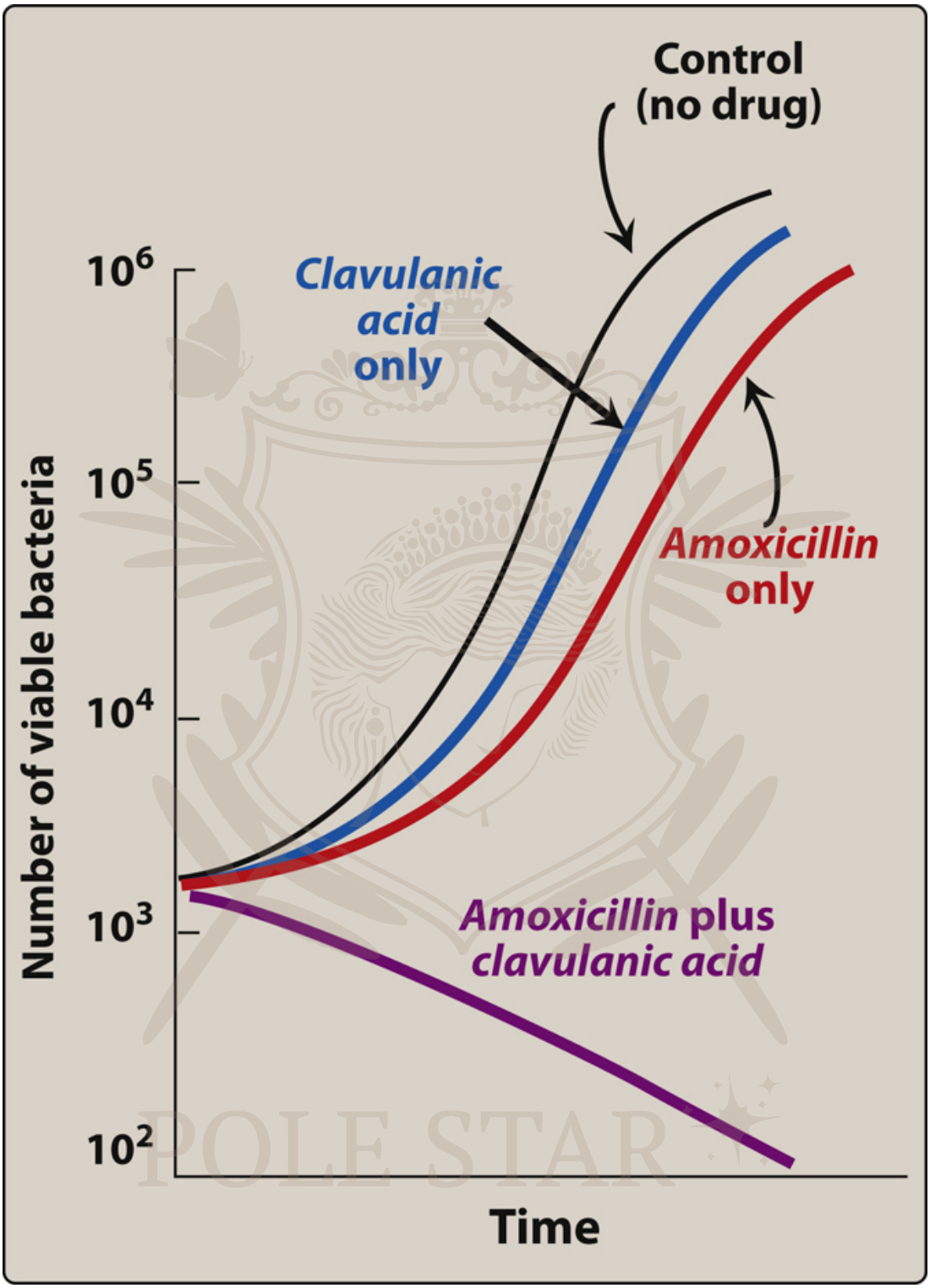

Figure 29.16 The in vitro growth of Escherichia coli in the presence of *amoxicillin*, with and without *clavulanic acid*.

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A. Cephalosporin and β-Lactamase inhibitor combinations

Ceftolozane [sef-TOL-oh-zane] is a third-generation cephalosporin combined with the β-lactamase inhibitor, *tazobactam. Ceftolozane–tazobactam* is available only in an IV formulation. Its niche in therapy is in the treatment of resistant Enterobacterales and multidrug-resistant P. aeruginosa. *Ceftolozane–tazobactam* has activity against some β-lactamase–producing bacteria (for example, select strains of ESBLs). This combination has narrow gram-positive and very limited anaerobic activity. *Ceftazidime*, a third-generation cephalosporin, is combined with the β-lactamase inhibitor *avibactam* [AV-i-BAK-tam]. *Ceftazidime–avibactam*, available only in IV formulation, has broad gram-negative activity including Enterobacterales and P. aeruginosa. Addition of *avibactam* allows the drug to resist hydrolysis against broad-spectrum β-lactamases in Class A and C, with the exception of MBLs (Class B). Figure 29.17 displays the activity of various β-lactamase inhibitors against β-lactamases. *Ceftazidime–avibactam* has minimal activity against Acinetobacter as well as anaerobic and gram-positive organisms. Both of these combinations are indicated for the treatment of intra-abdominal infections (in combination with *metronidazole*) and for the management of complicated urinary tract infections. Given the extensive antimicrobial activity, *ceftolozane–tazobactam* and *ceftazidime–avibactam* are reserved for the treatment of infections due to multidrug-resistant pathogens.

	Class A	Class B	Class C	Class D
Examples of enzymes	KPC, SHV, TEM, CTX-M	MBL	AmpC	OXA
Inhibitor activity	*Tazobactam* Avibactam Vaborbactam Relebactam*	None	*Avibactam Vaborbactam Relebactam*	*Avibactam** Vaborbactam Relebactam***

Figure 29.17 Activity of new β-lactamase inhibitors against β-lactamase enzymes.*Inhibits most enzymes except KPC. **Variable activity.
AmpC = AmpC β-lactamase; CTX-M = CTX-M β-lactamase; KPC = Klebsiella pneumoniae carbapenemase; MBL = metallo-β-lactamase; OXA = OXA-type β-lactamase.

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B. Carbapenem/β-Lactamase inhibitor combinations

Meropenem–vaborbactam and *imipenem–cilastatin–relebactam* are combinations of a carbapenem and a non–β-lactam β-lactamase inhibitor. *Meropenem–vaborbactam* is approved for the treatment of complicated urinary tract infections including pyelonephritis. In addition to these indications, *imipenem–cilastatin–relebactam* is also approved for the treatment of hospital-acquired pneumonia and ventilator-associated pneumonia. *Relebactam* is structurally similar to *avibactam.* The structure of *vaborbactam* contains boronic acid which increases the activity of *meropenem* against Class A β-lactamases. Both *vaborbactam* and *relebactam* have activity against Enterobacterales producing a broad spectrum of β-lactamases, with the exception of MBLs (Figure 29.18).

Agent	Activity Against β-Lactam Resistant Gram-Negative Organisms
Ceftolozane/tazobactam	• Pseudomonas aeruginosa* • ESBL-producing isolates • No activity against carbapenemases
Ceftazidime/avibactam	• CRE* (including KPC-producing isolates, variable activity against OXA, no activity against MBLs) • Pseudomonas aeruginosa* • ESBL and AmpC-producing isolates
Cefiderocol	• CRE* (all carbapenemases including MBLs) • Pseudomonas aeruginosa • Acinetobacter baumannii • Stenotrophomonas maltophilia • ESBL and AmpC-producing isolates
Meropenem/vaborbactam	• CRE* (including KPC-producing isolates, no activity against OXA or MBLs) • ESBL and AmpC-producing isolates • *Vaborbactam* does not enhance activity against carbapenem-resistant Pseudomonas aeruginosa or Acinetobacter due to efflux/porin mutations
Imipenem/cilastatin/relebactam	• CRE* (including KPC-producing isolates, less active against OXA, no activity against MBLs) • Pseudomonas aeruginosa* • ESBL and AmpC-producing isolates

Figure 29.18 Place in therapy of novel β-lactam agents.*Primary role in therapy. AmpC = AmpC β-lactamase; CRE= carbapenem-resistant Enterobacterales; ESBL = extended-spectrum β-lactamase; KPC = Klebsiella pneumoniae carbapenemase; MBL = metallo-β-lactamase; OXA = OXA-type β-lactamase.

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VI. VANCOMYCIN

Vancomycin [van-koe-MYE-sin] is a tricyclic glycopeptide active against aerobic and anaerobic gram-positive bacteria, including MRSA, *methicillin*-resistant Staphylococcus epidermidis, Enterococcus spp., and C. difficile (Figure 29.19). Following cell entry, it binds to peptidoglycan precursors, disrupting polymerization and cross-linking required for maintenance of cell wall integrity. This interaction results in bactericidal activity. Due to an increased incidence of MRSA, *vancomycin* is commonly used in patients with skin and soft tissue infections, infective endocarditis, and nosocomial pneumonia. The frequency of administration for *vancomycin* is dependent on renal function. Therefore, monitoring of creatinine clearance is required to optimize drug exposure and minimize toxicity. Optimal cure rates are observed when trough concentrations are maintained between 10 and 20 µg/mL. [Note: The ratio of the area under the curve to the minimum inhibitory concentration (AUC/MIC ratio) is the best predictor of *vancomycin* activity against S. aureus, with an AUC/MIC of greater than or equal to 400 associated with treatment success.] Initial trough concentrations are obtained prior to the fourth or fifth *vancomycin* dose to ensure appropriate dosing. Common adverse events include nephrotoxicity, infusion-related reactions (*vancomycin* infusion reaction characterized by histamine release, flushing, and sometimes anaphylactoid reactions); phlebitis, and ototoxicity. Emergence of resistance is uncommon within Streptococcus and Staphylococcus spp., but frequently observed in Enterococcus faecium infections. Resistance in Enterococci is driven by alterations in binding affinity to peptidoglycan precursors and occurs in the presence of the VanA gene. Due to the prevalence of resistance, prudent use of *vancomycin* is warranted. Lastly, *vancomycin* has poor absorption after oral administration, so use of the oral formulation is limited to the management of C. difficile infection in the colon.

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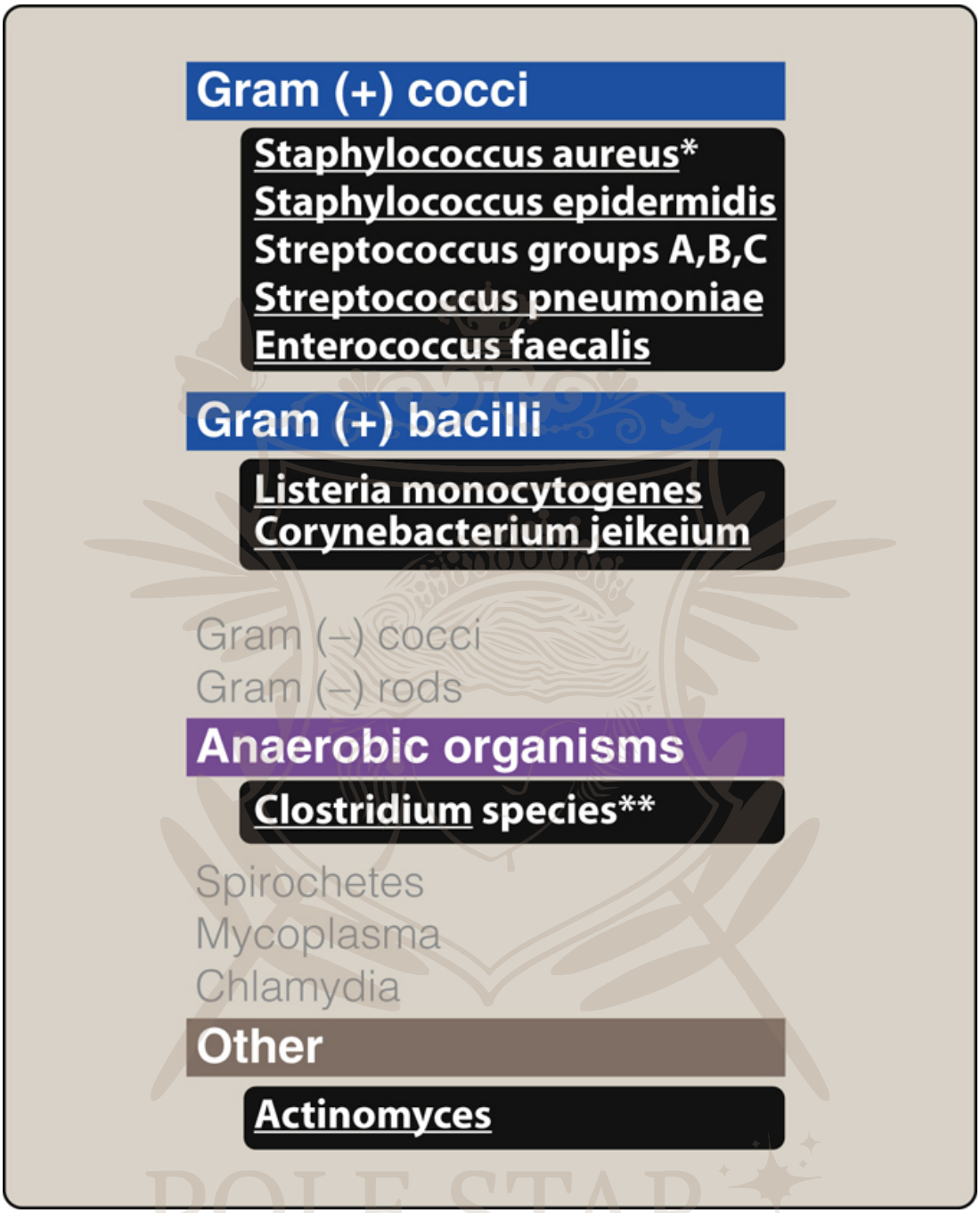

Figure 29.19 Antimicrobial spectrum of *vancomycin*. *Includes *methicillin*-resistant strains. **Oral *vancomycin* only for Clostridioides difficile.

VII. LIPOGLYCOPEPTIDES

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Telavancin [tel-a-VAN-sin], *oritavancin* [or-IT-a-VAN-sin], and *dalbavancin* [dal-ba-VAN-sin] are semisynthetic lipoglycopeptide antibiotics with bactericidal, concentration-dependent activity against gram-positive bacteria. The lipoglycopeptides maintain a spectrum of activity similar to *vancomycin*, affecting primarily staphylococci, streptococci, and enterococci. Because of structural differences, they are more potent than *vancomycin* and may have activity against *vancomycin*-resistant isolates. Like *vancomycin*, these agents inhibit bacterial cell wall synthesis. The lipid tail is essential in anchoring the drug to the cell walls to improve target site binding. Additionally, *telavancin* and *oritavancin* disrupt membrane potential. In combination, these actions improve activity and minimize selection of resistance. *Telavancin* is considered an alternative to *vancomycin* in treating acute bacterial skin and skin structure infections (ABSSSIs) and hospital-acquired pneumonia caused by resistant gram-positive organisms, including MRSA. The use of *telavancin* in clinical practice is limited by the adverse effect profile, which includes nephrotoxicity, risk of fetal harm, and interactions with medications known to prolong the QT_c interval (for example, fluoroquinolones, macrolides). Prior to initiation, assessment of renal function, pregnancy status, and current medications is needed to ensure safe administration.

In contrast to *telavancin*, *oritavancin* and *dalbavancin* have prolonged half-lives (245 and 204 hours, respectively), allowing for single-dose IV administration for the management of ABSSSI. Stable patients with ABSSSI may be treated as outpatients, eliminating the need for inpatient admission, central catheter placement, and/or daily outpatient parenteral antibiotic therapy. Consistent with other glycopeptides, infusion-related reactions may occur. *Oritavancin* and *telavancin* are known to interfere with phospholipid reagents used in assessing coagulation. Alternative therapy should be considered with concomitant *heparin* use.

VIII. DAPTOMYCIN

Daptomycin [DAP-toe-mye-sin] is a cyclic lipopeptide antibiotic with bactericidal, concentration-dependent activity. It is indicated as an alternative to other agents, such as *vancomycin or linezolid*, for the treatment of infections caused by resistant gram-positive organisms,

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including MRSA and *vancomycin*-resistant enterococci (Figure 29.20). *Daptomycin* is indicated for the treatment of complicated skin and skin structure infections and bacteremia caused by *S. aureus*, including those with right-sided infective endocarditis. Efficacy of treatment with *daptomycin* in left-sided endocarditis has not been demonstrated. Additionally, *daptomycin* is inactivated by pulmonary surfactants; thus, it should *never* be used in the treatment of pneumonia. *Daptomycin* is dosed IV once daily and the frequency of dosing should be adjusted in renal dysfunction. Figure 29.21 provides a comparison of important characteristics of *vancomycin*, *daptomycin*, *telavancin*, and the long-acting lipoglycopeptides.

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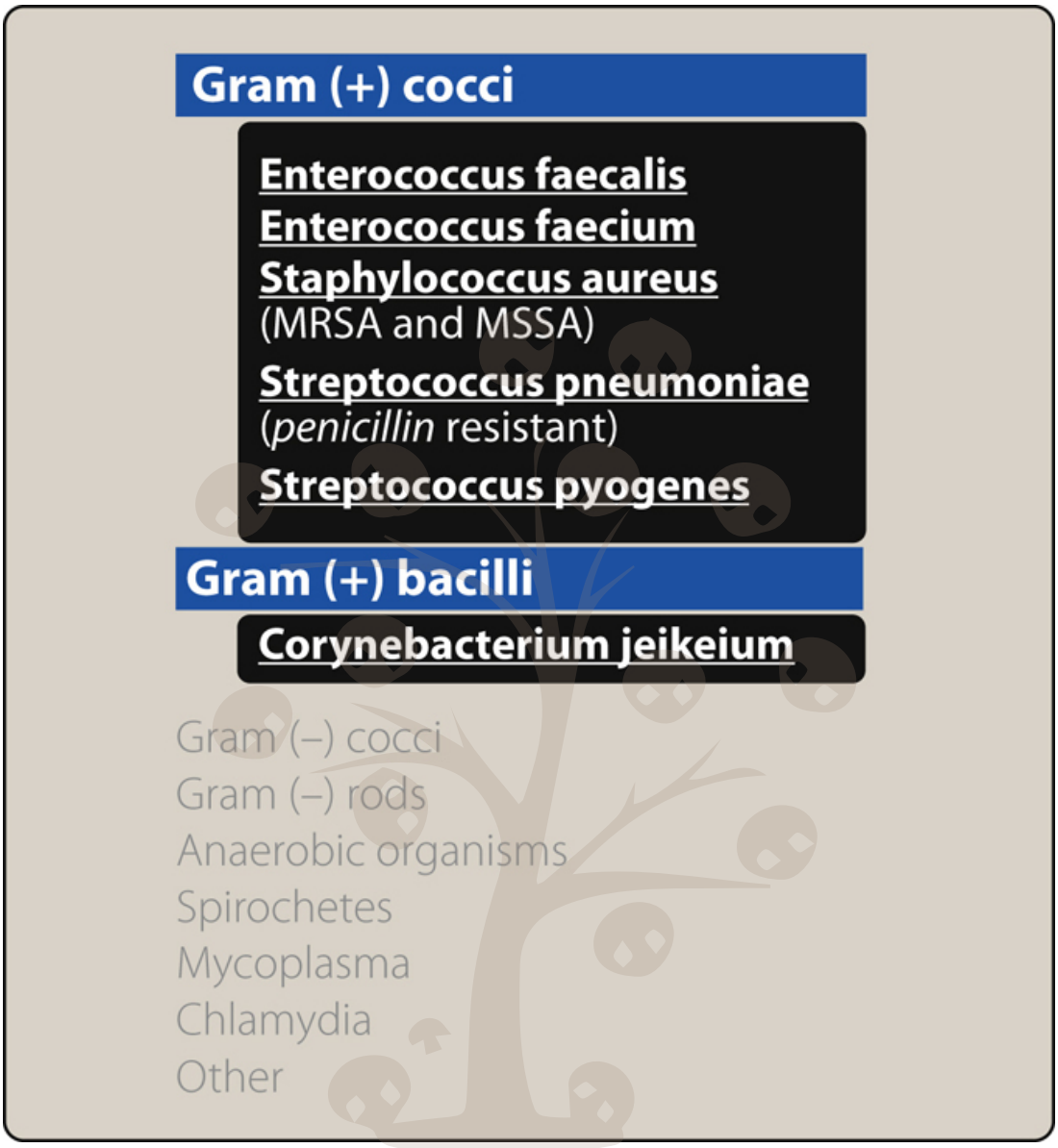

Figure 29.20 Antimicrobial spectrum of *daptomycin*.MRSA = *methicillin*-resistant Staphylococcus aureus; MSSA = *methicillin*-susceptible Staphylococcus aureus.

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	VANCOMYCIN	DAPTOMYCIN	TELAVANCIN	DALBAVANCIN	ORITAVANCIN
Mechanism of Action	Inhibits bacterial cell wall synthesis	Causes rapid depolarization of cell membrane, inhibits DNA, RNA, and protein synthesis	Inhibits bacterial cell wall synthesis; disrupts cell membrane	Inhibits bacterial cell wall synthesis	Inhibits bacterial cell wall synthesis; disrupts cell membrane
Pharmacodynamics		Concentration-dependent Bactericidal	Concentration-dependent Bactericidal	Concentration-dependent Bactericidal	Concentration-dependent Bactericidal
Common Antibacterial Spectrum	Activity limited to gram-positive organisms: Staphylococcus aureus (including MRSA), Streptococcus pyogenes, S. agalactiae, *penicillin*-resistant S. pneumoniae, Corynebacterium jeikeium, *vancomycin*-susceptible Enterococcus faecalis, and E. faecium				
Unique Antibacterial Spectrum	*Clostridioides difficile* (oral only)	VRE	Some VRE isolates	VISA and some VRE	VISA, VRSA, and VRE
Route	IV/PO	IV	IV	IV	IV
Administration Time	60- to 90-min IV infusion	2-min IV push 30-min IV infusion	60-min IV infusion	30-min IV infusion	3-hr IV infusion
Pharmacokinetics	Renal elimination Half-life: 6–10 hours Dose is adjusted based on renal function and serum trough levels	Renal elimination Half-life: 7–8 hours Dose is adjusted based on renal function	Renal elimination Half-life: 7–9 hours Dose is adjusted based on renal function	Renal elimination Half-life: 204 hours	Renal elimination Half-life: 245 hours Dose is adjusted based on renal function
Unique Adverse Effects	Infusion-related reactions due to histamine release: fever, chills, phlebitis, flushing; dose-related ototoxicity and nephrotoxicity	Elevated hepatic transaminases and CPK (check weekly), myalgias and rhabdomyolysis (consider holding HMG-CoA reductase inhibitors [statins] while on therapy)	Taste disturbances, foamy urine, QTc prolongation, interferes with coagulation labs (PT/INR, aPTT, ACT), not recommended in pregnancy (box warning recommends pregnancy test prior to initiation)	Infusion-related reactions; elevated hepatic transaminases	Infusion-related reactions; elevated hepatic transaminases Screen for drug interactions; inhibitor and inducer of P450 enzymes; increases *warfarin* concentrations
Key Learning Points	Drug of choice for severe MRSA infections; oral form only used for C. difficile; monitor serum trough concentrations for safety and efficacy	*Daptomycin* is inactivated by pulmonary surfactants and should never be used in the treatment of pneumonia	Use with caution in patients with baseline renal dysfunction (CrCl < 50 mL/min) due to higher rates of treatment failure in clinical studies; coagulation labs should be drawn prior to the *telavancin* dose to avoid interaction	Single-dose administration; may be used in outpatient or ED setting to avoid hospital admission for patients with ABSSSI	Single-dose administration; may be used in outpatient or ED setting to avoid hospital admission for patients with ABSSSI; coagulation labs should be drawn prior to the *oritavancin* dose to avoid interaction

Figure 29.21 Side-by-side comparison of *vancomycin*, *daptomycin*, and *telavancin*, and the long-acting lipoglycopeptides.ABSSSI = acute bacterial skin and skin structure infections; CPK = creatine phosphokinase; CrCl = creatinine clearance; ED = emergency department; IV = intravenous; MRSA = *methicillin*-resistant Staphylococcus aureus; VISA = *vancomycin*-intermediate Staphylococcus aureus; VRE = *vancomycin*-resistant enterococci; VRSA = *vancomycin*-resistant Staphylococcus aureus.

IX. FOSFOMYCIN

Fosfomycin [fos-foe-MYE-sin] is a synthetic derivative of phosphonic acid. It blocks cell wall synthesis by inhibiting the enzyme enolpyruvyl transferase, a key step in peptidoglycan synthesis, and exhibits

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bactericidal activity. It is indicated for urinary tract infections caused by E. coli or E. faecalis and is considered first-line therapy for acute cystitis. Due to its unique structure and mechanism of action, cross-resistance with other antimicrobial agents is unlikely. *Fosfomycin* is rapidly absorbed after oral administration and distributes well to the kidneys, bladder, and prostate. The drug is excreted in its active form in the urine and maintains high concentrations over several days, allowing for a one-time dose. [Note: A parenteral formulation is available in select countries and has been used for the treatment of systemic infections.] The most commonly reported adverse effects include diarrhea, vaginitis, nausea, and headache.

X. POLYMYXINS

The polymyxins are cation polypeptides that bind to phospholipids on the bacterial cell membrane of gram-negative bacteria. They have a detergent-like effect that disrupts cell membrane integrity, leading to leakage of cellular components and cell death. Polymyxins are concentration-dependent bactericidal agents with activity against most clinically important gram-negative bacteria, including P. aeruginosa, E. coli, K. pneumoniae, Acinetobacter spp., and Enterobacter spp. However, alterations in the cell membrane and lipid polysaccharides allow many species of Proteus and Serratia to be intrinsically resistant. Only two forms of polymyxin are in clinical use today, *polymyxin B* and *colistin* (*polymyxin E*). *Polymyxin B* is available in parenteral, ophthalmic, otic, and topical preparations. *Colistin* is only available as a prodrug, *colistimethate sodium*, which is administered IV or inhaled via a nebulizer. The use of these drugs has been limited due to the increased risk of nephrotoxicity and neurotoxicity (for example, slurred speech, muscle weakness) when used systemically. However, in the setting of gram-negative resistance, they may be used as salvage therapy for patients with multidrug-resistant infections and limited alternative therapeutic options. Careful dosing and monitoring of adverse effects are important to maximize the safety and efficacy of these agents.

Chapter Summary

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- Cell wall active antibiotics exert their bactericidal activity by interfering with cell wall synthesis.
- A four-membered β-lactam ring is common to all β-lactam antibiotics.
- *Penicillin* has limited activity against gram-negative bacteria due to resistance from β-lactamase production.
- Structural modifications to the β-lactam produce cephalosporins and carbapenems which have a broader spectrum of activity as compared to *penicillin.*
- Addition of β-lactamase inhibitors improves the activity of antibiotics by hydrolyzing β-lactamase enzymes produced by the bacteria.
- *Vancomycin* is the drug of choice for a variety of gram-positive bacteria, particularly *methicillin*-resistant Staphylococcus aureus (MRSA).
- Long-acting lipoglycopeptides (for example, *oritavancin* and *dalbavancin*) have prolonged half-lives which allow for single-dose administration.
- *Daptomycin* is ineffective for the treatment of pneumonia due to inactivation by pulmonary surfactants.
- Polymyxins are reserved for the treatment of multidrug-resistant pathogens.

STUDY QUESTIONS

Choose the ONE best answer.

29.1 A 23-year-old man presents with acute appendicitis that ruptures shortly after admission. He is taken to the operating room for surgery, and postsurgical cultures reveal *Escherichia coli* and *Bacteroides fragilis*, susceptibilities pending. Which of the following provides adequate empiric coverage of these two pathogens?

A. Cefepime
B. Piperacillin/tazobactam
C. Aztreonam
D. Ceftaroline

Correct answer = B. While all of these agents cover most strains of E. coli, piperacillin/tazobactam is the only drug on this list that provides coverage against *Bacteroides* species.

29.2 A 68-year-old man presents from a nursing home with fever, increased urinary frequency and urgency, and mental status changes. He has a penicillin allergy of anaphylaxis. Which of the

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following β-lactams is the most appropriate choice for gram-negative coverage of this patient's urinary tract infection?

A. Cefepime
B. Ertapenem
C. Aztreonam
D. Ceftaroline

Correct answer = C. Based on the severity of the allergic reaction, aztreonam is the choice of all the β-lactams. Although cross-reactivity with cephalosporins and carbapenems is low, the risk rarely outweighs the benefit in these cases.

29.3 A 25-year-old man presents to the urgent care center with a painless sore on his genitals that started 2 weeks ago. He reports unprotected sex with a new partner about a month ago. A blood test confirms the patient has *Treponema pallidum.* Which of the following is the drug of choice for the treatment of this patient's-infection as a single dose?

A. Benzathine penicillin G
B. Ceftriaxone
C. Aztreonam
D. Vancomycin

Correct answer = A. A single treatment with penicillin is curative for primary and secondary syphilis. No antibiotic resistance has been reported, and it remains the drug of choice unless the patient has a severe allergic reaction.

29.4 Which of the following cephalosporins has activity against gram-negative anaerobic pathogens like *Bacteroides fragilis*?

A. Cefoxitin
B. Cefepime
C. Ceftriaxone
D. Cefazolin

Correct answer = A. The cephamycins (cefoxitin and cefotetan) are the only cephalosporins with in vitro activity against anaerobic gram-negative pathogens.

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Cefepime, ceftriaxone, and cefazolin have no appreciable activity against *Bacteroides fragilis*.

29.5 In which of the following cases would it be appropriate to use telavancin?

A. A 29-year-old pregnant woman with ventilator-associated pneumonia
B. A 76-year-old man with hospital-acquired pneumonia also receiving amiodarone for atrial fibrillation
C. A 36-year-old man with cellulitis and abscess growing MRSA
D. A 72-year-old woman with a diabetic foot infection growing MRSA who has moderate renal dysfunction

Correct answer = C. A is not a good option due to the potential of telavancin harming the fetus. Option B is not a good choice because the patient is on amiodarone, and telavancin can cause QT_c prolongation. Option D is not an appropriate choice because the patient has baseline renal dysfunction and telavancin should be avoided unless the benefit outweighs the risk. Option C is the best choice since telavancin is approved for skin and skin structure infections, and the patient has no apparent contraindication.

29.6 Which of the following genes produces a change in the PBP rendering treatment with penicillin ineffective?

A. VanA
B. mecA
C. KPC
D. AmpC

Correct answer = B. The mecA gene alters PBPs which makes penicillin treatment ineffective. MRSA occurs due to the presence of the mecA gene in *Staphylococcus aureus.* VanA is the gene responsible for resistance to vancomycin in Enterococci. KPC and AmpC are examples of β-lactamases.

29.7 An elderly homeless patient who is known to be noncompliant with medications presents to the Emergency Department with an uncomplicated skin and soft tissue infection. Which of the following

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antibiotics can be used to treat the infection and avoid hospitalization?

A. Daptomycin
B. Ceftaroline
C. Vancomycin
D. Oritavancin

Correct answer = D. All options can be used to treat skin and soft tissue infections. However, oritavancin is a long-acting lipoglycopeptide and can be administered as a single dose, thereby preventing hospitalization.

29.8 Which of the following best describes the reason imipenem is co-formulated with cilastatin?

A. To protect imipenem from β-lactamases
B. To reduce hypersensitivity reactions associated with imipenem
C. To protect imipenem from renal dehydropeptidase
D. To reduce the metabolism of imipenem

Correct answer = C. Imipenem undergoes cleavage by a dehydropeptidase found in the brush border of the proximal renal tubule. Compounding imipenem with cilastatin protects the parent drug from renal dehydropeptidase and, thus, prolongs its activity in the body.

29.9 A patient in the medical intensive care unit is receiving cefepime for the treatment of a urinary tract infection. The cefepime dose was adjusted due to declining renal function. On day 4 of hospitalization, the urine culture is positive for *Proteus mirabilis.* Which of the following is most appropriate based on the susceptibility profile below and the patient's clinical status?

Antibiotic	**Susceptible (S), Intermediate (I), Resistant (R)**
Ceftriaxone	R
Cefepime	R
Piperacillin/tazobactam	S
Colistin	S

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A. Continue cefepime
B. Switch to colistin
C. Switch to piperacillin/tazobactam
D. Switch to ceftriaxone

Correct answer = C. Although both colistin and piperacillin/tazobactam are appropriate choices since the bacteria is susceptible, piperacillin/tazobactam is a safer selection since colistin is highly associated with nephrotoxicity and the patient already has declining renal function.

29.140 75-year-old man is diagnosed with ventilator-associated pneumonia. A bronchoalveolar lavage is performed and respiratory culture grows carbapenem-resistant *Escherichia coli* that is found to produce metallo-β-lactamase. Which of the following agents is most likely to have activity against this organism?

A. Ceftolozane/tazobactam
B. Cefiderocol
C. Meropenem/vaborbactam
D. Cefepime

Correct answer = B. Cefiderocol is the only antibiotic listed that has activity against all carbapenemases, including metallo-β-lactamases. In addition, cefiderocol is indicated for the treatment of ventilator-associated pneumonia. The remaining antibiotics listed do not provide activity against metallo-β-lactamase–producing organisms.

POLE STAR

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30

Protein Synthesis Inhibitors

Lindsey M. Childs-Kean

I. OVERVIEW

A number of antibiotics exert their antimicrobial effects by targeting bacterial ribosomes and inhibiting bacterial protein synthesis. Most of these agents exhibit bacteriostatic activity. Bacterial ribosomes differ structurally from mammalian cytoplasmic ribosomes and are composed of 30S and 50S subunits (mammalian ribosomes have 40S and 60S subunits). In general, selectivity for bacterial ribosomes minimizes potential adverse consequences encountered with the disruption of protein synthesis in mammalian host cells. However, high concentrations of drugs such as *chloramphenicol* or the tetracyclines may cause toxic effects as a result of interaction with mitochondrial mammalian ribosomes, since the structure of mitochondrial ribosomes more closely resembles bacterial ribosomes. Figure 30.1 summarizes the antimicrobial protein synthesis inhibitors discussed in this chapter.

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TETRACYCLINES

Demeclocycline DECLOMYCIN
Doxycycline DORYX, VIBRAMYCIN
Eravacycline XERAVA
Minocycline MINOCIN
Omadacycline NUZYRA
Tetracycline GENERIC ONLY

GLYCYLCYCLINES

Tigecycline TYGACIL

AMINOGLYCOSIDES

Amikacin GENERIC ONLY
Gentamicin GENERIC ONLY
Neomycin GENERIC ONLY
Plazomicin ZEMDRI
Streptomycin GENERIC ONLY
Tobramycin TOBI, TOBREX

MACROLIDES

Azithromycin ZITHROMAX
Clarithromycin BIAXIN
Erythromycin E.E.S., ERY-TAB

MACROCYCLIC

Fidaxomicin DIFICID

LINCOSAMIDES

Clindamycin CLEOCIN

OXAZOLIDINONES

Linezolid ZYVOX
Tedizolid SIVEXTRO

PLEUROMUTILIN

Lefamulin XENLETA

OTHERS

Chloramphenicol GENERIC ONLY
Quinupristin/Dalfopristin SYNERCID

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Figure 30.1 Summary of protein synthesis inhibitors.

II. TETRACYCLINES

Tetracyclines consist of four fused rings with a system of conjugated double bonds. Substitutions on these rings alter the individual pharmacokinetics and spectrum of antimicrobial activity.

A. Mechanism of action

Tetracyclines enter susceptible organisms via passive diffusion and by an energy-dependent transport protein mechanism unique to the bacterial inner cytoplasmic membrane. Tetracyclines concentrate intracellularly in susceptible organisms. The drugs bind reversibly to the 30S subunit of the bacterial ribosome. This action prevents binding of tRNA to the mRNA–ribosome complex, thereby inhibiting bacterial protein synthesis (Figure 30.2).

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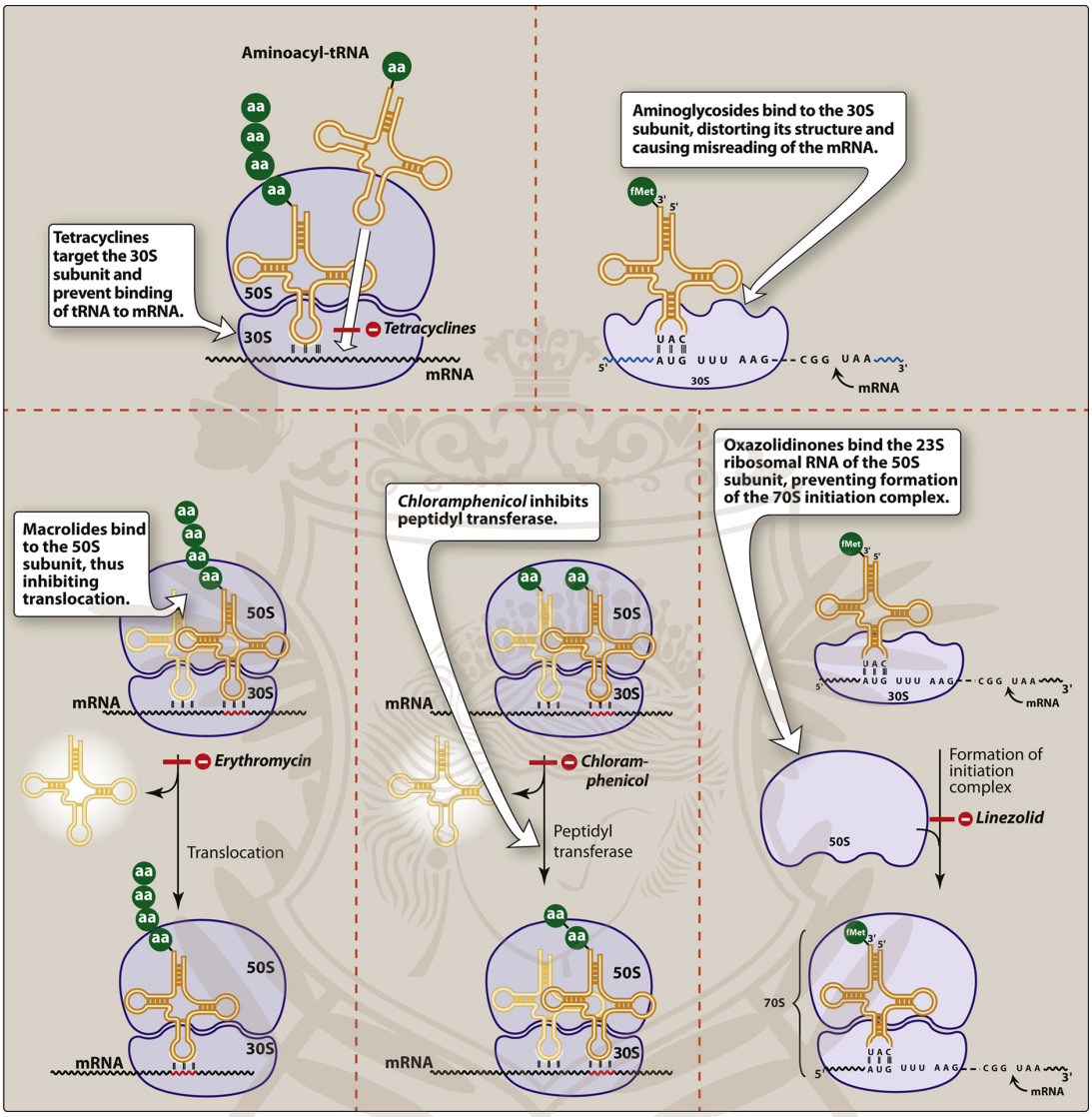

Figure 30.2 Mechanisms of action of the various protein synthesis inhibitors.aa = amino acid.

B. Antibacterial spectrum

The tetracyclines are bacteriostatic antibiotics effective against a wide variety of organisms, including gram-positive and gram-negative bacteria, protozoa, spirochetes, mycobacteria, and atypical species. They are commonly used in the treatment of acne and *Chlamydia* infections (Figure 30.3).

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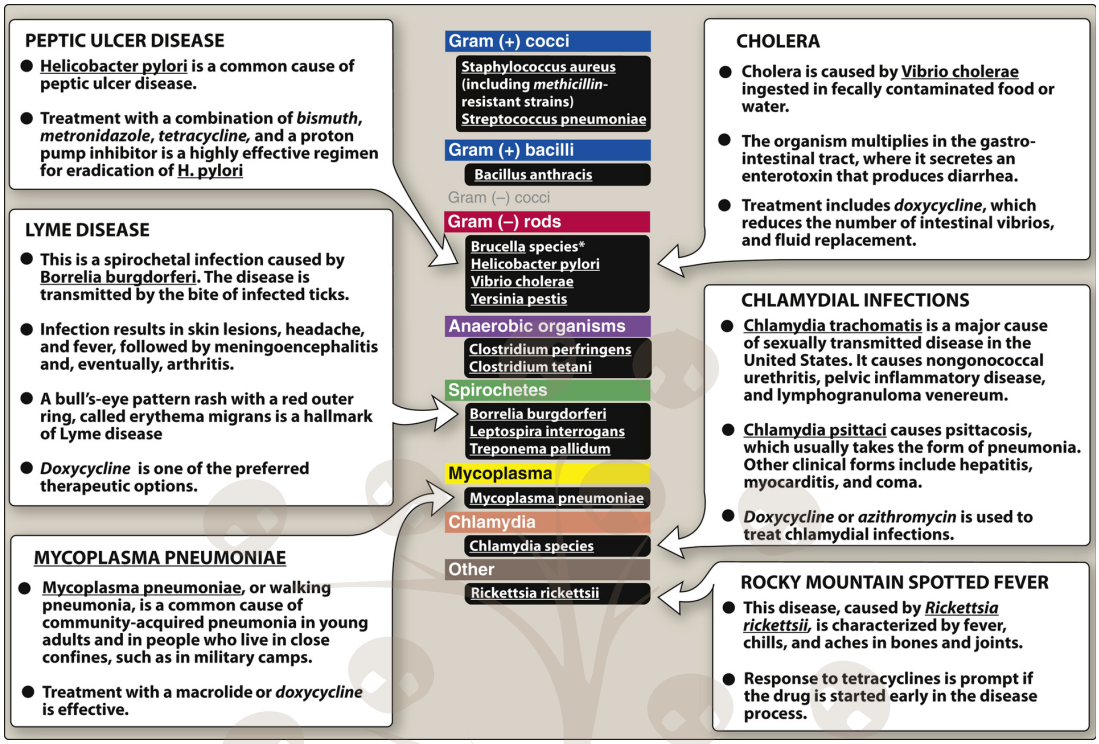

Figure 30.3 Typical therapeutic applications of tetracyclines.*A *tetracycline + gentamicin*.

C. Resistance

The most commonly encountered naturally occurring resistance to tetracyclines is an efflux pump that expels drug out of the cell, thus preventing intracellular accumulation. Other mechanisms of bacterial resistance to tetracyclines include enzymatic inactivation of the drug and production of bacterial proteins that prevent tetracyclines from binding to the ribosome. Resistance to one tetracycline does not confer universal resistance to all tetracyclines, and the development of cross-resistance may be dependent on the mechanism of resistance.

D. Pharmacokinetics

1. Absorption: Tetracyclines are adequately absorbed after oral ingestion (Figure 30.4). Administration with substances that contain divalent and trivalent cations (for example,

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magnesium, calcium and aluminum antacids, or iron supplements) decreases absorption, particularly for *tetracycline* [tet-rah-SYE-kleen], due to the formation of nonabsorbable chelates (Figure 30.5). *Tetracycline* and *omadacycline* [oh-mah-dah-SYE-kleen] should not be administered with dairy products, but dairy products do not affect absorption of *doxycycline* [dox-i-SYE-kleen] or *minocycline* [min-oh-SYE-kleen]. *Doxycycline* [dox-i-SYE-kleen], *minocycline* [min-oh-SYE-kleen], and *omadacycline* are available as oral and intravenous (IV) preparations. *Eravacycline* [err-ah-vah-SYE-kleen] is only available in IV preparation.

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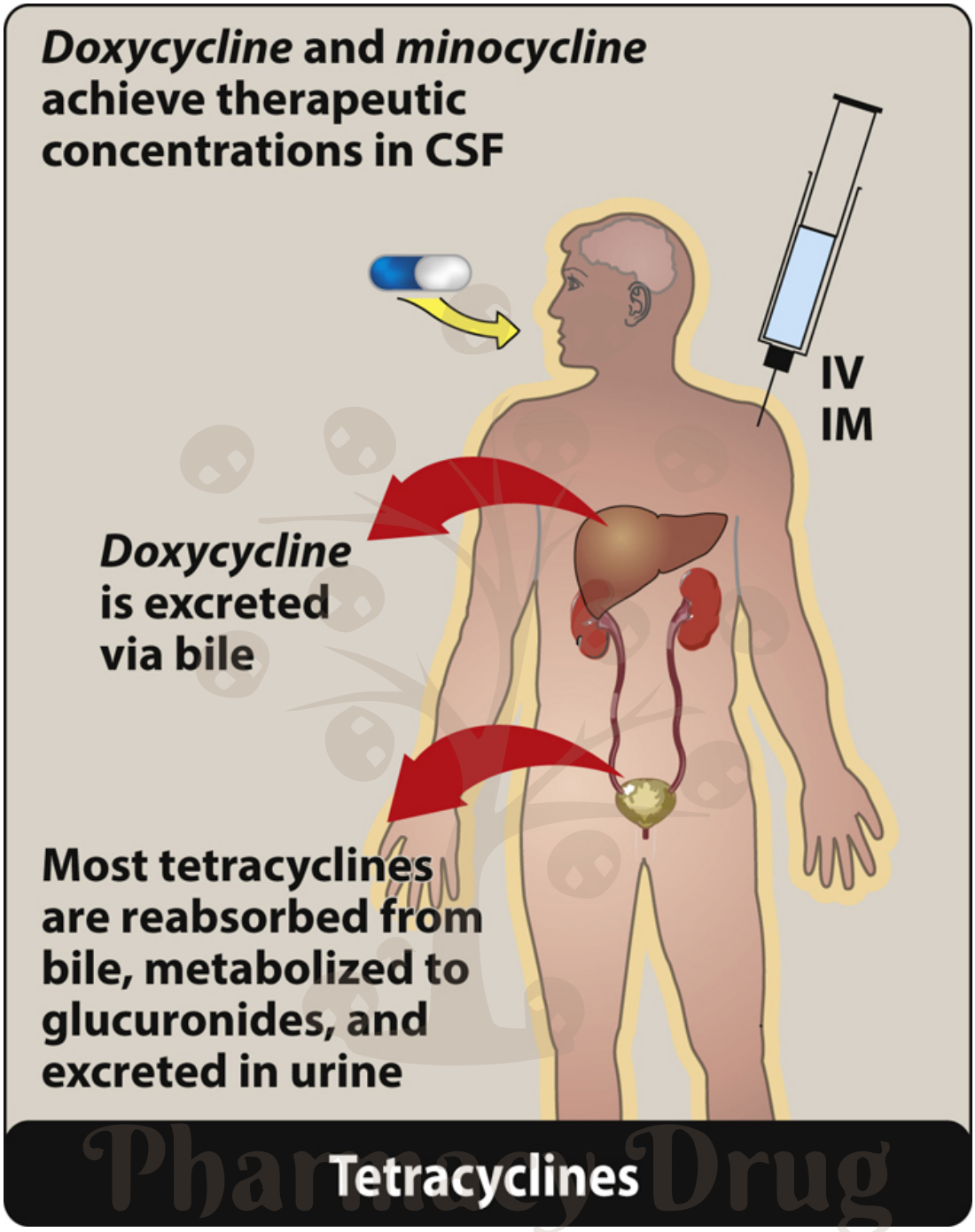

Figure 30.4 Administration and fate of tetracyclines.CSF = cerebrospinal fluid.

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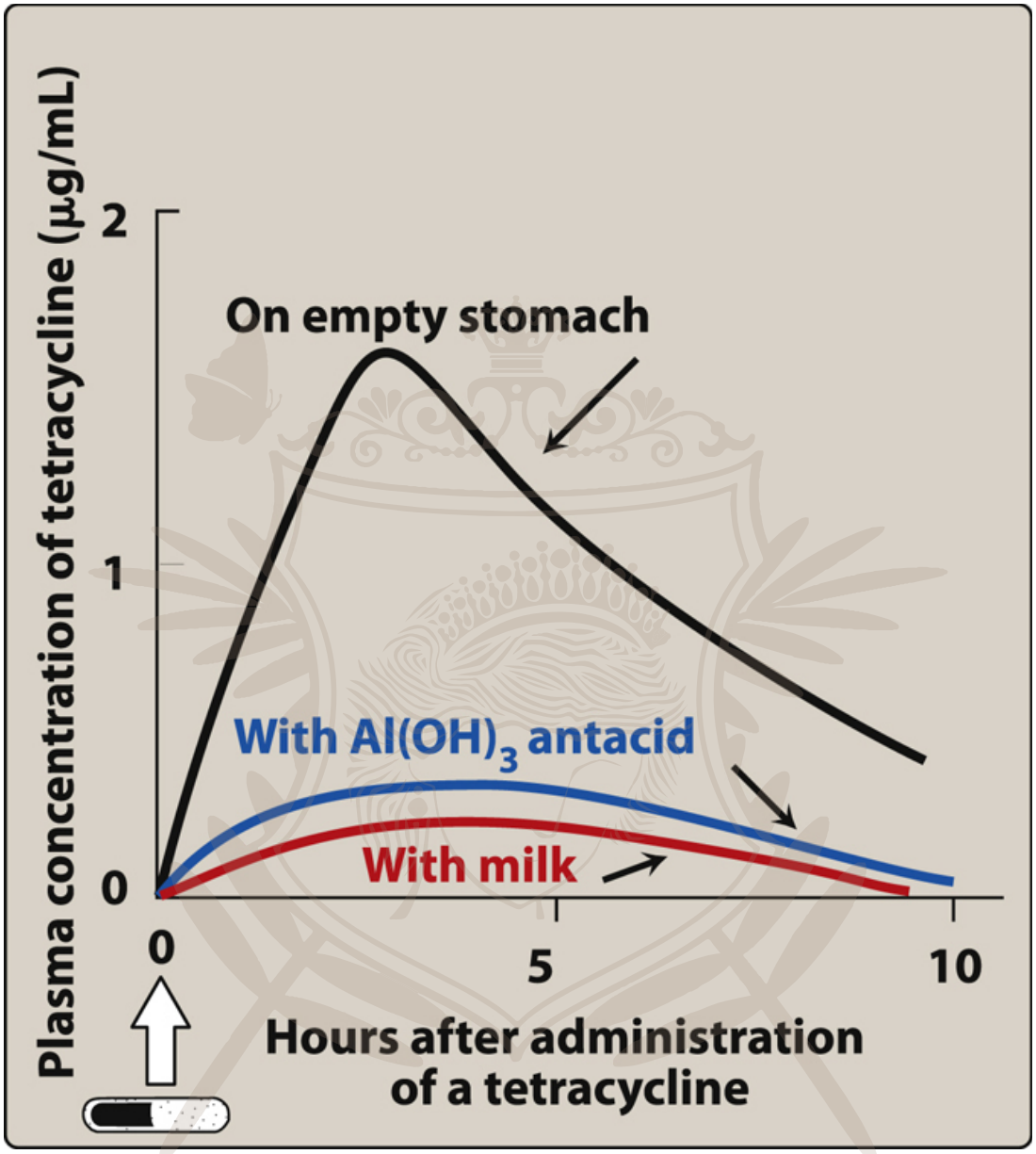

Figure 30.5 Effect of antacids and milk on the absorption of tetracyclines.Data from P. J.Neuvonen , K. T.Kivisto , and P.Lehto . *Clin. Pharm. Ther*. 50: 499 (1991).

2.Distribution: The tetracyclines concentrate well in the bile, liver, kidney, gingival fluid, and skin. Moreover, they bind to tissues undergoing calcification (for example, teeth and bones) or to tumors that have high calcium content. Penetration into most body fluids is adequate. Only

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minocycline and *doxycycline* achieve therapeutic levels in the cerebrospinal fluid (CSF). *Minocycline* also achieves high concentrations in saliva and tears, rendering it useful in eradicating the meningococcal carrier state. All tetracyclines cross the placental barrier and concentrate in fetal bones and dentition.

3.Elimination: *Tetracycline* is primarily excreted unchanged in the urine, whereas *minocycline* undergoes hepatic metabolism and is eliminated to a lesser extent via the kidney. *Doxycycline* is preferred in patients with renal dysfunction, as it is primarily eliminated via the bile into the feces.

E. Adverse effects

1.Gastric discomfort: Epigastric distress commonly results from irritation of the gastric mucosa (Figure 30.6) and is often responsible for noncompliance with tetracyclines. Esophagitis may be minimized through coadministration with food (other than dairy products) or fluids and the use of capsules rather than tablets. [Note: *Tetracycline* and *omadacycline* should be taken on an empty stomach.]

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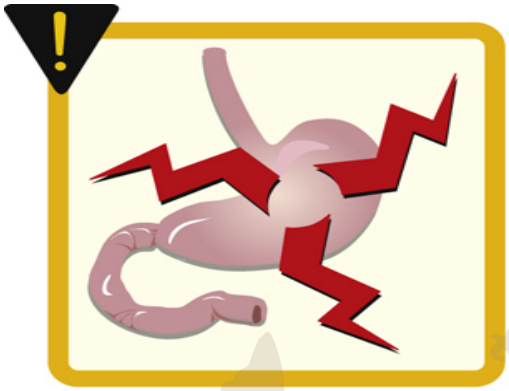
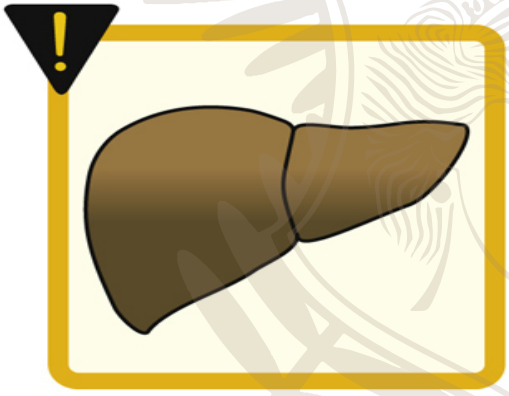


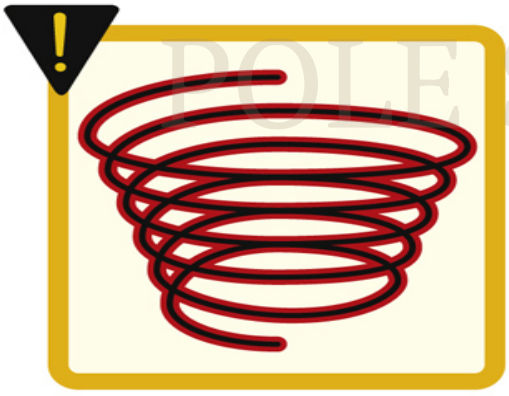
GI disturbance

Deposition of drug in bones and teeth



Liver failure

Phototoxicity



Vertigo

Avoid in pregnancy

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Figure 30.6 Some adverse effects of tetracyclines.GI = gastrointestinal.

2.Effects on calcified tissues: Deposition of tetracyclines in the bone and primary dentition occurs during the calcification process in growing children. This may cause discoloration and hypoplasia of teeth and a temporary stunting of growth. For this reason, the use of tetracyclines is limited in pediatrics.

3.Hepatotoxicity: Rarely hepatotoxicity may occur with high doses, particularly in pregnant women and those with preexisting hepatic dysfunction or renal impairment.

4.Phototoxicity: Severe sunburn may occur in patients receiving a tetracycline who are exposed to sun or ultraviolet rays. This toxicity is encountered with any tetracycline, but more frequently with *tetracycline* and *demeclocycline* [dem-e-kloe-SYE-kleen]. Patients should be advised to wear adequate sun protection.

5.Other effects: Benign, intracranial hypertension (pseudotumor cerebri) characterized by headache and blurred vision may occur rarely in adults. Although discontinuation of the drug reverses this condition, it is not clear whether permanent sequelae may occur. Vestibular dysfunction manifested as dizziness, vertigo, and tinnitus may occur, particularly with *minocycline*.

6.Contraindications: The tetracyclines should not be used in pregnant or breastfeeding women or in children less than 8 years of age.

Clinical Application 30.1: Doxycycline for Lyme Disease

Lyme disease is caused by the bacteria *Borrelia burgdorferi* after a tick bite and is endemic to many parts of the northern United States. Lyme disease can

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cause localized reactions, including erythema migrans, a characteristic red ring-like rash, as well as disseminated symptoms, including arthritis, pericarditis/myocarditis, and meningitis/encephalitis. In areas where Lyme disease is highly endemic, one dose of *doxycycline* can be given as post-exposure prophylaxis after a documented tick bite. *Doxycycline* is the treatment of choice for Lyme disease. The duration of therapy is 10 days in early Lyme disease and 2 to 4 weeks for disseminated infection.

III. GLYCYLCYCLINES

Tigecycline [tye-ge-SYE-kleen], a derivative of *minocycline*, is the only member of the glycylcycline antimicrobial class. It is indicated for the treatment of complicated skin and soft tissue infections, complicated intra-abdominal infections, and community-acquired pneumonia.

A. Mechanism of action

Tigecycline exhibits bacteriostatic action by reversibly binding to the 30S ribosomal subunit and inhibiting bacterial protein synthesis.

B. Antibacterial spectrum

Tigecycline exhibits broad-spectrum activity that includes *methicillin*-resistant Staphylococcus aureus (MRSA), multidrug-resistant streptococci, *vancomycin*-resistant enterococci (VRE), extended-spectrum β-lactamase–producing gram-negative bacteria, Acinetobacter baumannii, and many anaerobic organisms. *Tigecycline* is not active against Morganella, Proteus, Providencia, or Pseudomonas species.

C. Resistance

Tigecycline was developed to overcome the emergence of tetracycline class–resistant organisms that utilize efflux pumps and ribosomal protection to confer resistance. Resistance to

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tigecycline has been observed and is primarily attributed to overexpression of efflux pumps.

D. Pharmacokinetics

Following IV infusion, *tigecycline* exhibits a large volume of distribution. It penetrates tissues well but achieves low plasma concentrations. Consequently, *tigecycline* is a poor option for bloodstream infections. The primary route of elimination is biliary/fecal. No dosage adjustments are necessary for patients with renal impairment; however, a dose reduction is recommended in severe hepatic dysfunction.

E. Adverse effects

Tigecycline is associated with significant nausea and vomiting. Acute pancreatitis, including fatality, has been reported with therapy. Elevations in liver enzymes and serum creatinine may also occur. All-cause mortality in patients treated with *tigecycline* is higher than with other agents. A boxed warning states that *tigecycline* should be reserved for use in situations when alternative treatments are not suitable. Other adverse effects are similar to those of the tetracyclines and include photosensitivity, pseudotumor cerebri, discoloration of permanent teeth when used during tooth development, and fetal harm when administered in pregnancy. *Tigecycline* may decrease the clearance of *warfarin.* Therefore, the international normalized ratio should be monitored closely when *tigecycline* is coadministered with *warfarin*.

Pharmacy Drug

IV. AMINOGLYCOSIDES

Aminoglycosides are used for the treatment of serious infections due to aerobic gram-negative bacilli; however, their clinical utility is limited due to serious toxicities.

A. Mechanism of action

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Aminoglycosides diffuse through porin channels in the outer membrane of susceptible organisms. These organisms also have an oxygen-dependent system that transports the drug across the cytoplasmic membrane. Inside the cell, they bind the 30S ribosomal subunit, where they interfere with assembly of the functional ribosomal apparatus and/or cause the 30S subunit of the completed ribosome to misread the genetic code (Figure 30.2). Aminoglycosides have concentration-dependent bactericidal activity; that is, their efficacy is dependent on the maximum concentration (C_{max}) of drug above the minimum inhibitory concentration (MIC) of the organism. For aminoglycosides, the target C_{max} is eight to ten times the MIC. They also exhibit a postantibiotic effect (PAE), which is continued bacterial suppression after drug concentrations fall below the MIC. The larger the dose, the longer the PAE. Because of these properties, high-dose extended-interval dosing is commonly utilized with aminoglycosides. This dosing strategy also reduces the risk of nephrotoxicity and increases convenience.

B. Antibacterial spectrum

The aminoglycosides are effective for the majority of aerobic gram-negative bacilli, including those that may be multidrug resistant, such as Pseudomonas aeruginosa, Klebsiella pneumoniae, and Enterobacter sp. Additionally, aminoglycosides are often combined with a β-lactam antibiotic to employ a synergistic effect, particularly in the treatment of Enterococcus faecalis and Enterococcus faecium infective endocarditis. Some therapeutic applications of four commonly used aminoglycosides —*amikacin* [am-i-KAY-sin], *gentamicin* [jen-ta-MYE-sin], *tobramycin* [toe-bra-MYE-sin], and *streptomycin* [strep-toe-MYE-sin]—are shown in Figure 30.7.

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TULAREMIA

- Tularemia is acquired during rabbit-hunting season by hunters skinning infected animals.
- Pneumonic tularemia results from infection by the respiratory route or by bacteremic seeding of lungs.
- *Gentamicin* is effective in treating this rare lymphoid disease.

SYNERGY

- Aminoglycosides may be added to β-lactams for synergy for select serious gram-positive infections.

Gram (+) cocci

- Enterococcus species (*ampicillin + gentamicin*)
- Streptococcus agalactiae (*ampicillin + gentamicin*)

Gram (+) bacilli
Gram (–) cocci

Gram (–) rods

- Acinetobacter baumannii
- Brucella species (*gentamicin + doxycycline*)
- Francisella tularensis (*gentamicin*)
- Klebsiella species
- Pseudomonas aeruginosa
- Yersinia pestis (*streptomycin*)

Anaerobic organisms
Spirochetes
Mycoplasma
Chlamydia
Other

INFECTIONS DUE TO PSEUDOMONAS AERUGINOSA

- Pseudomonas aeruginosa rarely attacks healthy individuals, but can cause infections in patients with specific risk factors (for example, recent antibiotic exposure, prolonged hospitalization, bronchiectasis).
- Treatment includes *tobramycin* alone (for example, for UTI) or in combination with an antipseudomonal β-lactam (for example, for pneumonia).

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Figure 30.7 Typical therapeutic applications of aminoglycosides.UTI = urinary tract infection.

C. Resistance

Resistance to aminoglycosides occurs via (1) efflux pumps, (2) decreased uptake, and/or (3) modification and inactivation by plasmid-associated synthesis of enzymes. Each of these enzymes has its own aminoglycoside specificity; therefore, cross-resistance cannot be presumed. *Amikacin* and *plazomicin* [plaz-oh-MYE-sin] are less vulnerable to these enzymes than other antibiotics in this group.

D. Pharmacokinetics

1.Absorption: The highly polar, polycationic structure of the aminoglycosides prevents adequate absorption after oral administration; therefore, all aminoglycosides (except *neomycin* [nee-oh-MYE-sin]) must be given parenterally to achieve adequate serum concentrations (Figure 30.8). [Note: *Neomycin* is not given parenterally due to severe nephrotoxicity. It is administered topically for skin infections or orally to decontaminate the gastrointestinal tract prior to colorectal surgery.]

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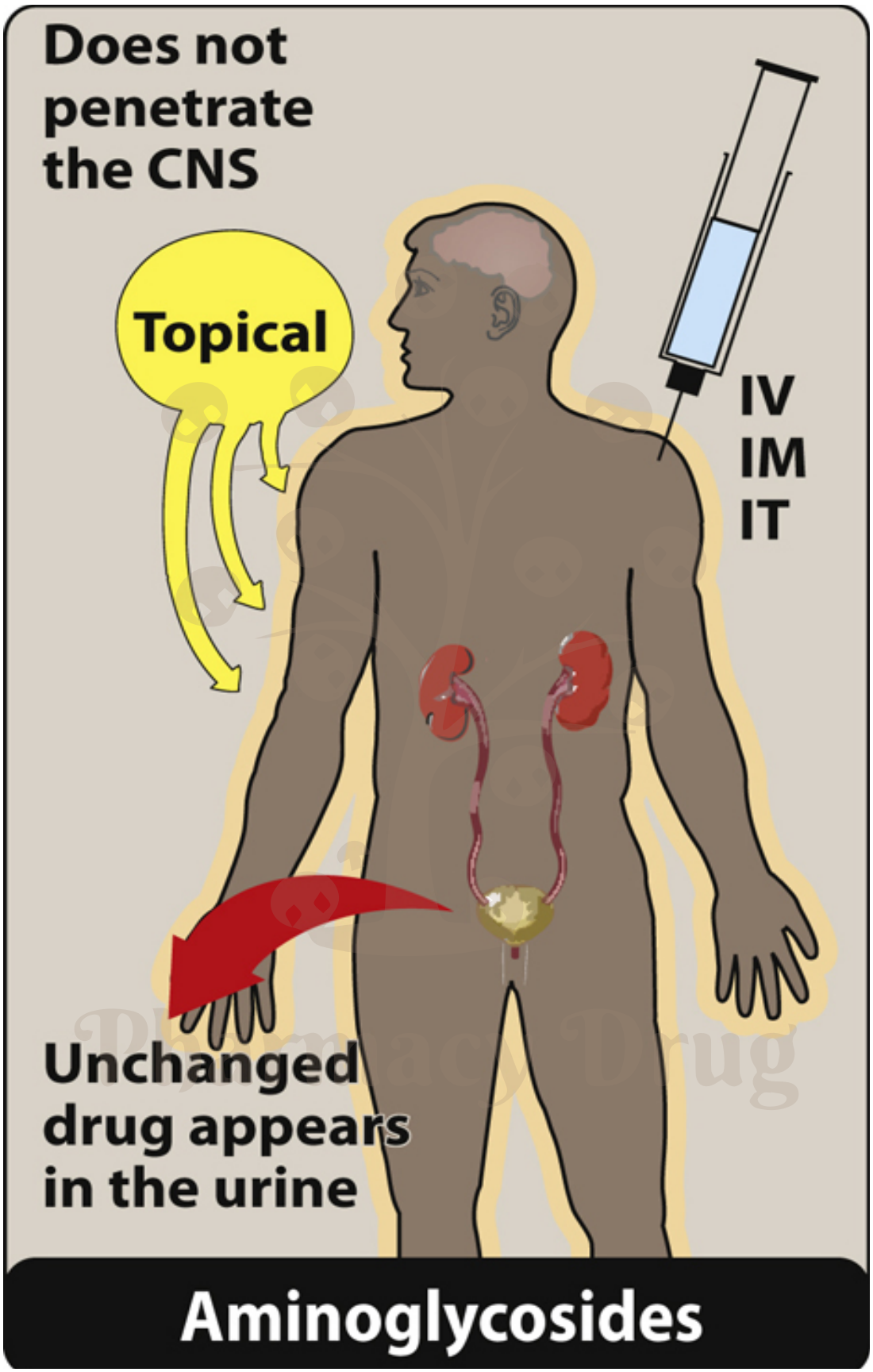

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Figure 30.8 Administration and fate of aminoglycosides.CNS = central nervous system.

2. Distribution: Because of their hydrophilicity, aminoglycoside tissue concentrations may be subtherapeutic, and penetration into most body fluids is variable. Concentrations achieved in CSF are inadequate, even in the presence of inflamed meninges. For central nervous system infections, the intrathecal or intraventricular routes may be utilized. All aminoglycosides cross the placental barrier and may accumulate in fetal plasma and amniotic fluid.

3. Elimination: More than 90% of the parenteral aminoglycosides are excreted unchanged in the urine (Figure 30.8). Accumulation occurs in patients with renal dysfunction; thus, dose adjustments are required. *Neomycin* is primarily excreted unchanged in the feces.

E. Adverse effects

Therapeutic drug monitoring of *gentamicin*, *tobramycin amikacin*, and *plazomicin* plasma concentrations is imperative to ensure appropriateness of dosing and to minimize dose-related toxicities (Figure 30.9). The elderly are particularly susceptible to-nephrotoxicity and ototoxicity.

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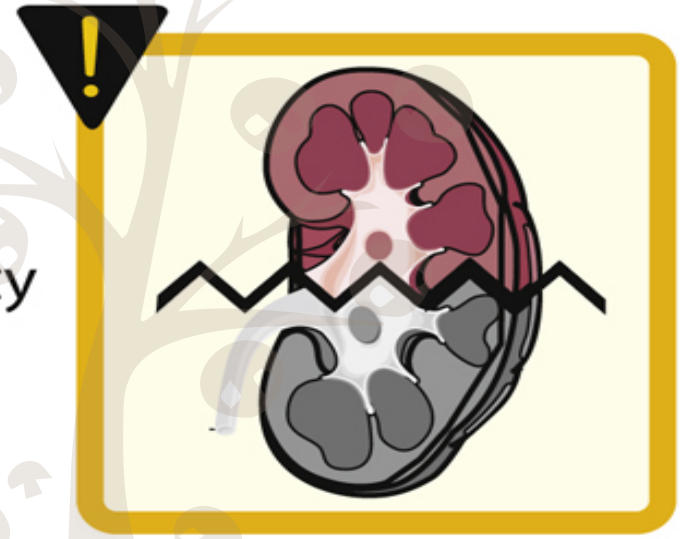
Ototoxicity

Nephrotoxicity



Skin rash

Pharmacy Drug

@Pharmacy_Z

Figure 30.9 Some adverse effects of aminoglycosides.

1. **Ototoxicity:** Ototoxicity (vestibular and auditory) is directly related to high peak plasma concentrations and the duration of treatment. Aminoglycosides accumulate in the endolymph and perilymph of the inner ear. Deafness may be irreversible and has been known to affect developing fetuses. Patients simultaneously receiving concomitant ototoxic drugs, such as *cisplatin* or loop diuretics, are particularly at risk. Vertigo (especially in patients receiving *streptomycin*) may also occur.

2. **Nephrotoxicity:** Retention of the aminoglycosides by the proximal tubular cells disrupts calcium-mediated transport processes. This results in kidney damage ranging from mild, reversible renal impairment to severe, potentially irreversible acute tubular necrosis.

3. **Neuromuscular blockade:** This adverse effect is associated with a rapid increase in concentration (for example, high doses infused over a short period) or concurrent administration with neuromuscular blockers. Patients with myasthenia gravis are particularly at risk. Prompt administration of *calcium gluconate* can reverse the block that causes neuromuscular paralysis.

4. **Allergic reactions:** Contact dermatitis is a common reaction to topically applied *neomycin.*

POLE STAR

V. MACROLIDES

The macrolides are a group of antibiotics with a macrocyclic lactone structure to which one or more deoxy sugars are attached. *Erythromycin* [er-ith-roe-MYE-sin] was the first of these drugs to have clinical application, both as a drug of first choice and as an alternative to *penicillin* in individuals with an allergy to β-lactam

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antibiotics. *Clarithromycin* [kla-rith-roe-MYE-sin] (a methylated form of *erythromycin*) and *azithromycin* [a-zith-roe-MYE-sin] (having a larger lactone ring) have some features in common with, and others that improve upon, *erythromycin*.

A. Mechanism of action

The macrolides bind irreversibly to a site on the 50S subunit of the bacterial ribosome, thus inhibiting translocation steps of protein synthesis (Figure 30.2). They may also interfere with other steps, such as transpeptidation. Generally considered to be bacteriostatic, they may be bactericidal at higher doses. Their binding site is either identical to or in close proximity to that for *clindamycin* and *chloramphenicol.*

B. Antibacterial spectrum

1. Erythromycin: This drug is effective against many of the same organisms as *penicillin G* (Figure 30.10); therefore, it may be considered as an alternative in patients with *penicillin* allergy.

Pharmacy Drug

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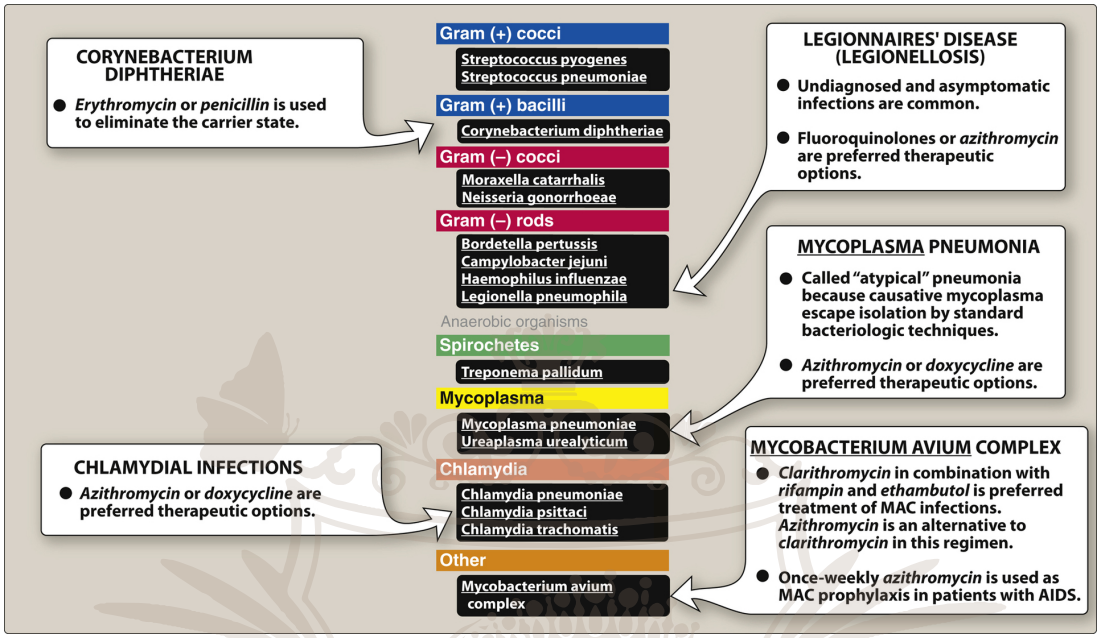

Figure 30.10 Typical therapeutic applications of macrolides.

2.Clarithromycin: *Clarithromycin* has activity similar to *erythromycin*, but it is also effective against Haemophilus influenzae and has greater activity against intracellular pathogens such as Chlamydia, Legionella, Moraxella, Ureaplasma species, and H. pylori. This drug also has activity against Mycobacterium avium complex.

3.Azithromycin: Although less active than *erythromycin* against streptococci and staphylococci, *azithromycin* is far more active against respiratory pathogens such as H. influenzae and Moraxella catarrhalis. Extensive use of *azithromycin* has resulted in growing Streptococcus pneumoniae resistance.

C. Resistance

Resistance to macrolides is associated with (1) the inability of the organism to take up the antibiotic, (2) the presence of efflux pumps, (3) a decreased affinity of the 50S ribosomal subunit for the antibiotic due to methylation of an adenine in the 23S bacterial

@pharmacy_drug2

ribosomal RNA in gram-positive organisms, and (4) the presence of plasmid-associated *erythromycin* esterases in gram-negative organisms such as the Enterobacteriaceae. *Erythromycin* has limited clinical use due to increasing resistance. Both *clarithromycin* and *azithromycin* share some cross-resistance with *erythromycin*.

D. Pharmacokinetics

1.Absorption: The *erythromycin* base is destroyed by gastric acid; thus, either enteric-coated tablets or esterified forms of the antibiotic are administered, and all have adequate oral absorption (Figure 30.11). *Clarithromycin* and *azithromycin* are stable in stomach acid and are readily absorbed. Food interferes with the absorption of *erythromycin* and *azithromycin* but can increase that of *clarithromycin. Erythromycin* and *azithromycin* are available in IV formulations.

Pharmacy Drug

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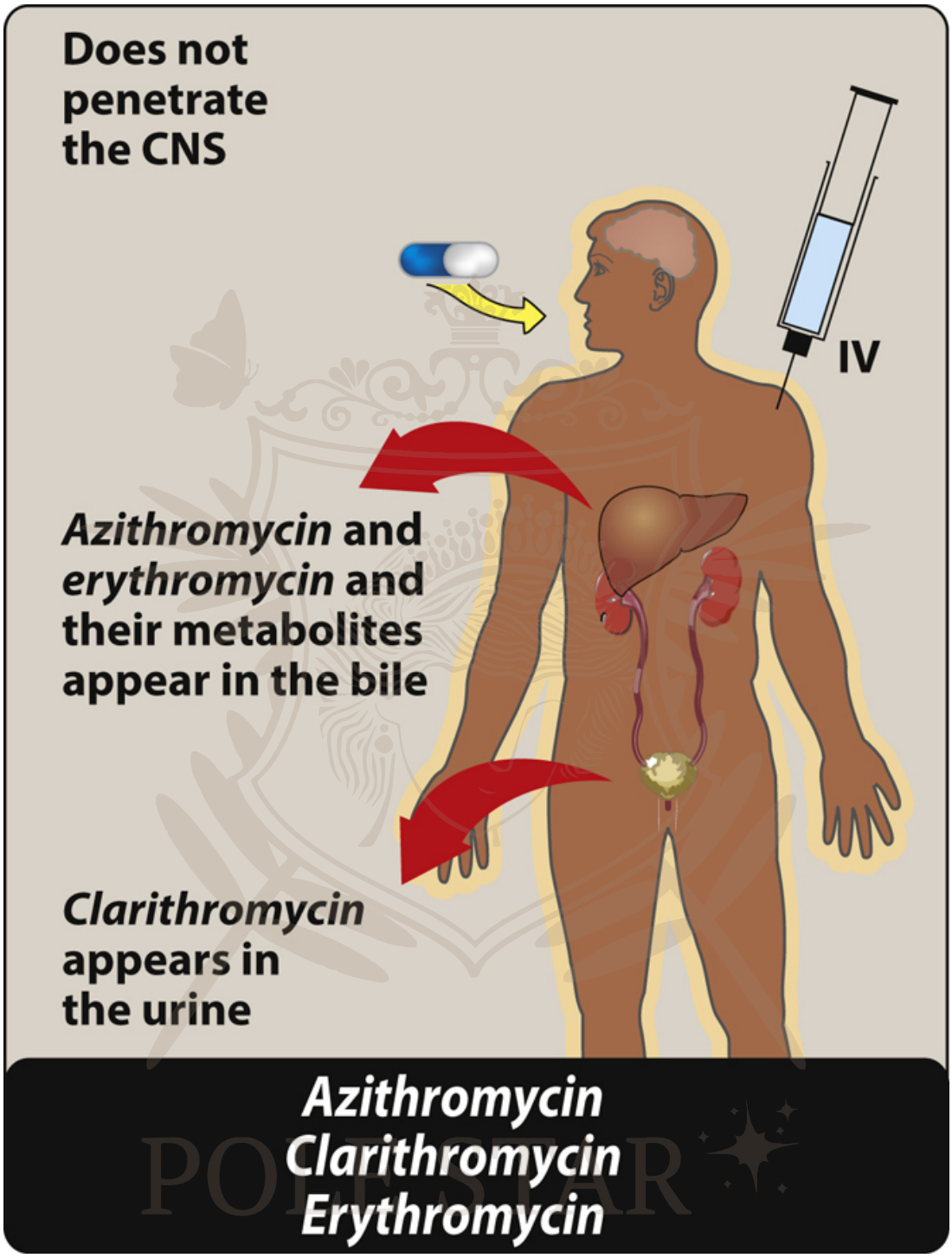

Figure 30.11 Administration and fate of the macrolide antibiotics.CNS = central nervous system.

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2.Distribution: *Erythromycin* distributes well to all body fluids except the CSF. It is one of the few antibiotics that diffuse into prostatic fluid, and it also accumulates in macrophages. All of the macrolides concentrate in the liver. *Clarithromycin* and *azithromycin* are widely distributed in the tissues. *Azithromycin* concentrates in neutrophils, macrophages, and fibroblasts, and serum concentrations are low. It has the largest volume of distribution of the macrolides.

3.Metabolism and excretion: *Azithromycin* is primarily concentrated and excreted in the bile as active drug. *Erythromycin* undergoes hepatic metabolism. *Erythromycin* and its metabolites are also excreted in the bile (Figure 30.11). Partial reabsorption occurs through the enterohepatic circulation. In contrast, *clarithromycin* is hepatically metabolized, and the active drug and its metabolites are mainly excreted in the urine (Figure 30.12). The dosage of this drug should be adjusted in patients with renal impairment.

Pharmacy Drug

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	Erythro-mycin	*Clarithro-mycin*	*Azithro-mycin*
Oral absorption	**Yes**	**Yes**	**Yes**
Half-life (hours)	**2**	**3.5**	**68**
Conversion to an active metabolite	**No**	**Yes**	**No**
Percent excretion in urine	**< 15**	**30–50**	**< 10**

Figure 30.12 Some properties of the macrolide antibiotics.

E. Adverse effects

1. Gastric distress and motility: Gastrointestinal upset is the most common adverse effect of the macrolides and may lead to poor patient compliance, especially with *erythromycin.* The other macrolides seem to be better tolerated (Figure 30.13). Higher doses of *erythromycin* lead to smooth muscle contractions that result in the movement of gastric contents to the duodenum, an adverse effect sometimes employed for the treatment of gastroparesis or postoperative ileus.

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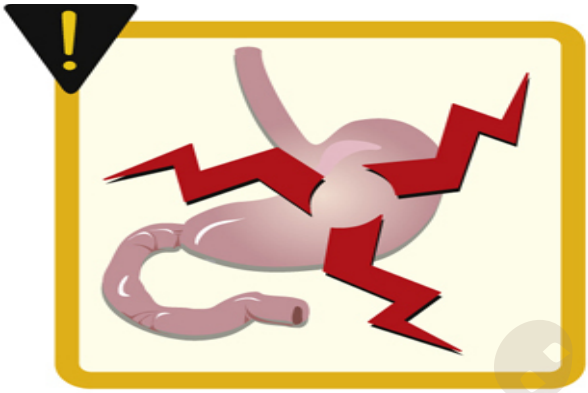
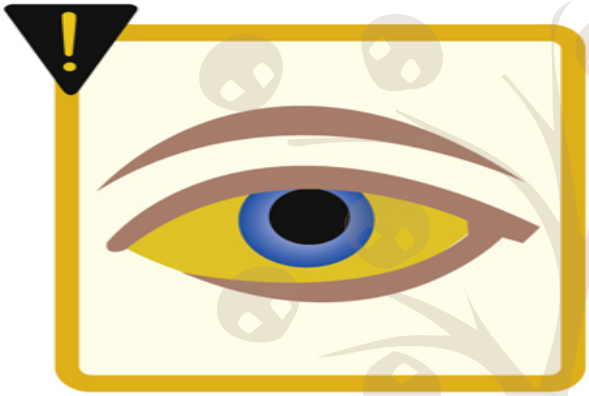
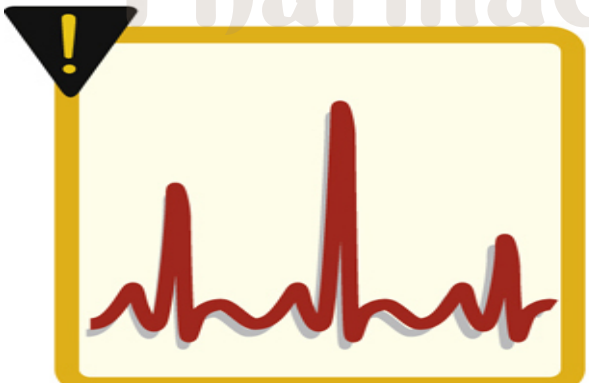


GI disturbance



Jaundice

Ototoxicity



QTc prolongation

Pharmacy Drug

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Figure 30.13 Some adverse effects of macrolide antibiotics.

2. Cholestatic jaundice: This adverse effect occurs most commonly with the estolate form of *erythromycin* (not used in the United States); however, it has been reported with other formulations and other agents in this class.

3. Ototoxicity: Transient hearing loss has been associated with *erythromycin*, especially at high dosages. *Azithromycin* has also been associated with irreversible sensorineural hearing loss.

4. QT_c prolongation: Macrolides may prolong the QT_c interval and should be used with caution in those patients with proarrhythmic conditions or concomitant use of proarrhythmic agents.

5. Contraindications: Patients with hepatic dysfunction should be treated cautiously with *erythromycin* or *azithromycin*, because these drugs accumulate in the liver.

6. Drug interactions: *Erythromycin* and *clarithromycin* inhibit the hepatic metabolism of a number of drugs, which can lead to toxic accumulation of these compounds (Figure 30.14). Both agents are inhibitors of CYP3A4 and the drug transporter P-glycoprotein. Interference with the metabolism of drugs such as *alfuzosin*, *alprazolam*, statins, and other agents metabolized by CYP3A4 has been reported for *clarithromycin*.

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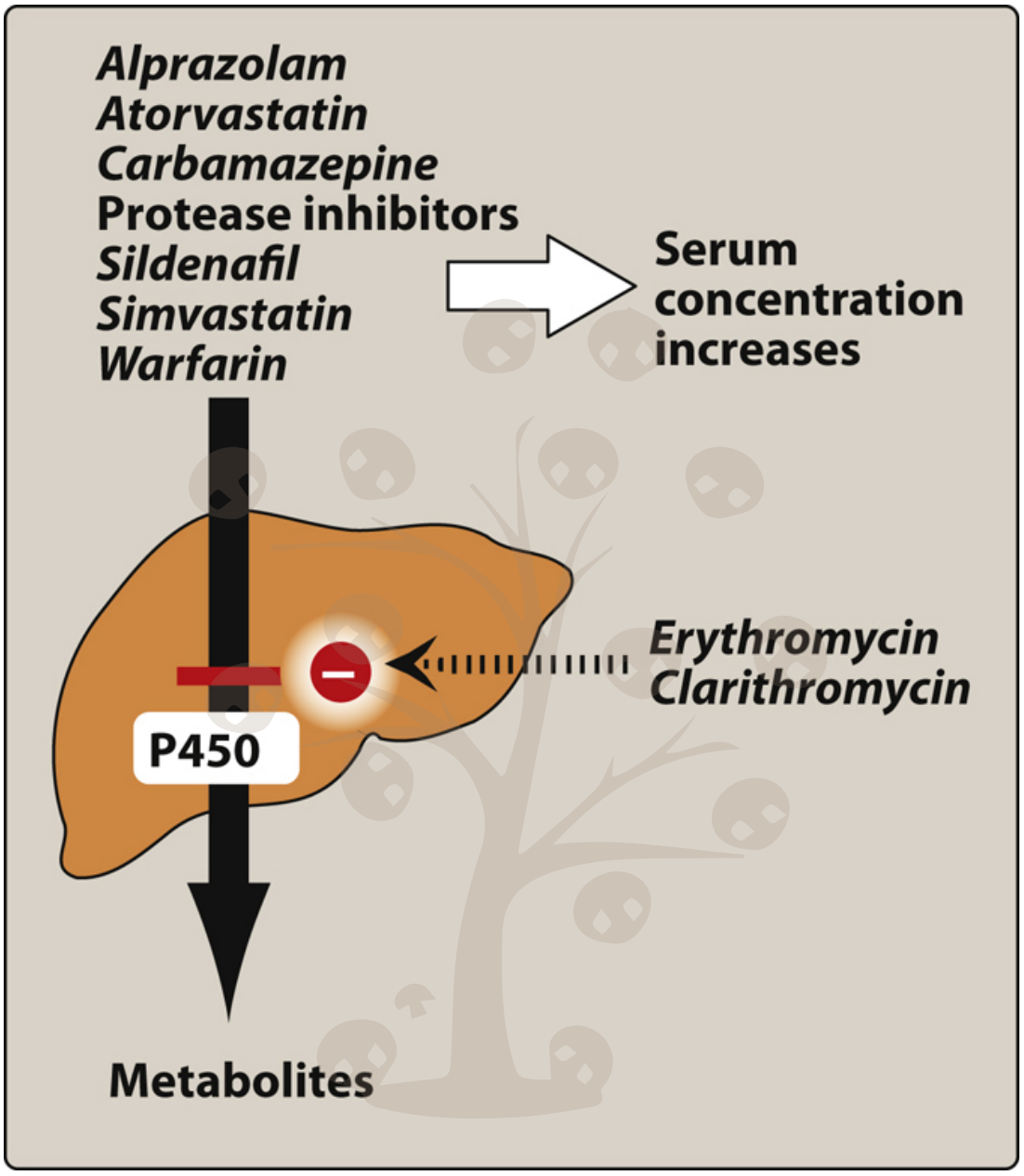

Figure 30.14 Inhibition of the cytochrome P450 system by *erythromycin* and *clarithromycin*.

Clinical Application 30.2: Immunomodulatory Activity of Macrolides

In addition to their antibacterial effects, macrolides also exhibit immunomodulatory properties. *Azithromycin*, in particular, has been shown to

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reduce the release of pro-inflammatory cytokines acutely and to help improve chronic inflammation long term. This is particularly notable in the epithelial cells in the lungs. This has led researchers and clinicians to explore the use of *azithromycin* for pulmonary diseases, such as community-acquired pneumonia, chronic obstructive pulmonary disease, and cystic fibrosis.

VI. FIDAXOMICIN

Fidaxomicin [fye-DAX-oh-MYE-sin] is a macrocyclic antibiotic with a structure similar to the macrolides; however, it has a unique mechanism of action. *Fidaxomicin* acts on the sigma subunit of RNA polymerase, thereby disrupting bacterial transcription, terminating protein synthesis, and resulting in cell death in susceptible organisms. *Fidaxomicin* has a very narrow spectrum of activity limited to gram-positive aerobes and anaerobes. It is used primarily for its bactericidal activity against Clostridioides difficile. Because of the unique target site, cross-resistance with other antibiotic classes has not been documented. Following oral administration, *fidaxomicin* has minimal systemic absorption and primarily remains within the gastrointestinal tract. This is ideal for the treatment of C. difficile infection, which occurs in the gut. The most common adverse effects include nausea, vomiting, and abdominal pain. Anemia and neutropenia have been observed infrequently. Hypersensitivity reactions including angioedema, dyspnea, and pruritus have occurred. *Fidaxomicin* should be used with caution in patients with a macrolide allergy, as they may be at increased risk for hypersensitivity.

POLE STAR

VII. CLINDAMYCIN

Clindamycin [klin-da-MYE-sin] has a mechanism of action that is similar to that of the macrolides. *Clindamycin* is used primarily in the treatment of infections caused by gram-positive organisms, including MRSA and Streptococcus sp., and anaerobic bacteria. Resistance

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mechanisms are the same as those for *erythromycin*, and cross-resistance has been described. C. difficile is resistant to *clindamycin*, and the utility of *clindamycin* for gram-negative anaerobes (for example, Bacteroides sp.) is decreasing due to increasing resistance. *Clindamycin* is available in IV, oral, topical, and vaginal formulations, but use of oral *clindamycin* is limited by gastrointestinal intolerance. [Note: Topical preparations of *clindamycin* are used for the treatment of acne (see Chapter 45), and vaginal formulations are used for the treatment of bacterial vaginosis.] After oral or intravenous administration, the drug distributes well into all body fluids but exhibits poor entry into the CSF. *Clindamycin* undergoes extensive oxidative metabolism to active and inactive products and is excreted into bile and urine. Low urinary excretion of active drug limits its clinical utility for urinary tract infections (Figure 30.15). Accumulation has been reported in patients with either severe renal impairment or hepatic failure. In addition to skin rash, the most common adverse effect is diarrhea, which may represent a serious pseudomembranous colitis caused by overgrowth of C. difficile. Oral administration of either *fidaxomicin* or *vancomycin* is usually effective in the treatment of C. difficile infection.

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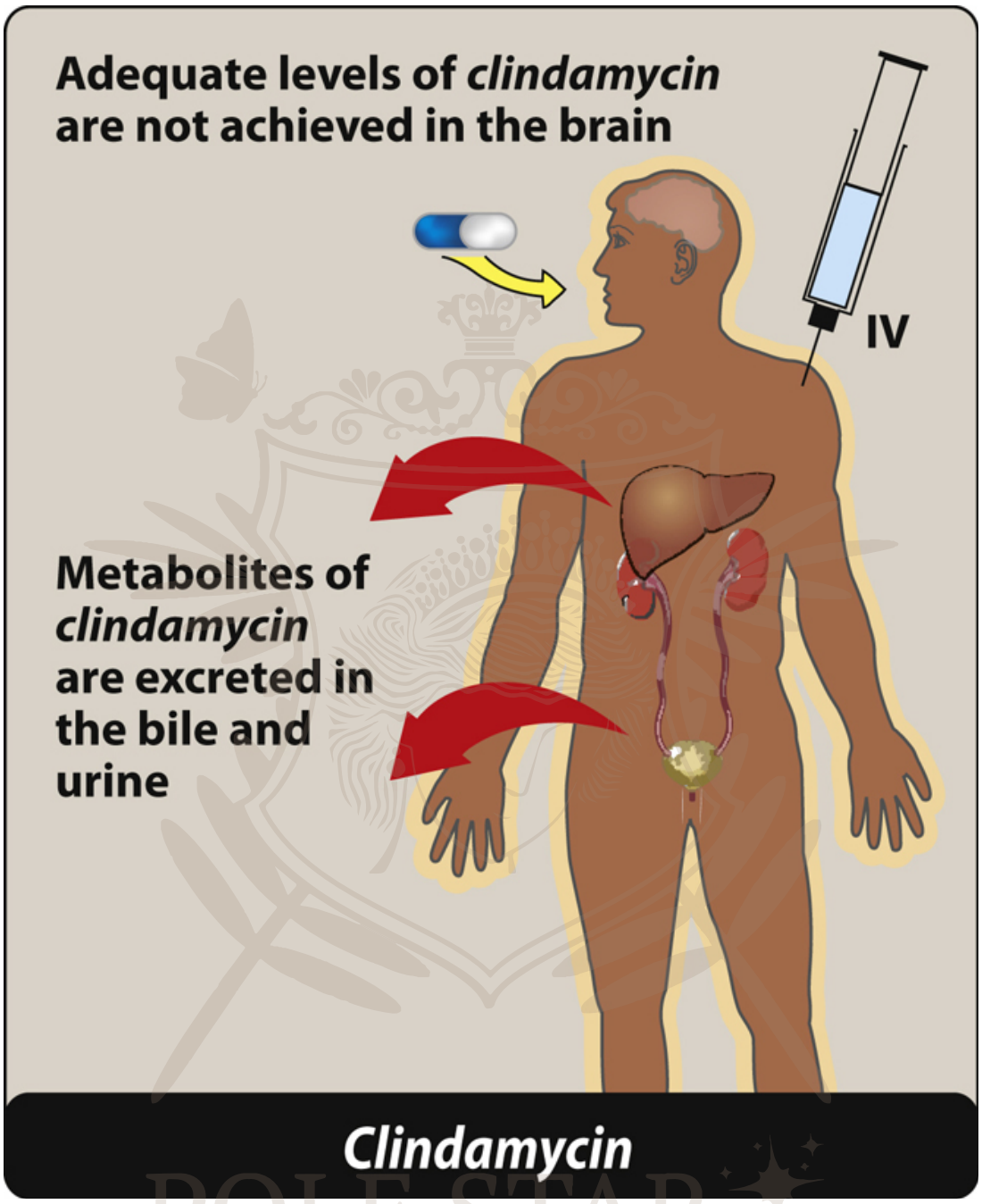

Figure 30.15 Administration and fate of *clindamycin*.

VIII. OXAZOLIDINONES

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Linezolid [lih-NEH-zo-lid] and *tedizolid* [ted-eye-ZOE-lid] are synthetic oxazolidinones developed to combat gram-positive organisms, including resistant isolates such as MRSA, VRE, and *penicillin*-resistant streptococci.

A. Mechanism of action

Linezolid and *tedizolid* bind to the bacterial 23S ribosomal RNA of the 50S subunit, thereby inhibiting the formation of the 70S initiation complex (Figure 30.2) and translation of bacterial proteins.

B. Antibacterial spectrum

The antibacterial action of the oxazolidinones is directed primarily against gram-positive organisms such as staphylococci, streptococci, and enterococci, Corynebacterium species, and Listeria monocytogenes. It is also moderately active against Mycobacterium tuberculosis (Figure 30.16). The main clinical use of *linezolid* and *tedizolid* is to treat infections caused by drug-resistant gram-positive organisms. Like other agents that interfere with bacterial protein synthesis, *linezolid* and *tedizolid* are bacteriostatic; however, *linezolid* has bactericidal activity against streptococci. *Linezolid* is an alternative to *daptomycin* for infections caused by VRE. Because they are bacteriostatic, the oxazolidinones are not recommended as first-line treatment for MRSA bacteremia.

Pharmacy Drug

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Gram (+) cocci

- Enterococcus faecalis (including *vancomycin*-resistant strains)
- Enterococcus faecium (including *vancomycin*-resistant strains)
- Staphylococcus aureus (including *methicillin*-resistant strains)
- Staphylococcus epidermidis (including *methicillin*-resistant strains)
- Staphylococcus haemolyticus
- Streptococcus pneumoniae (including *penicillin*-resistant strains)
- Viridans group streptococci

Gram (+) bacilli

- Corynebacterium species
- Listeria monocytogenes

Gram (–) cocci

Gram (–) rods

Anaerobic organisms

- Clostridium perfringens

Spirochetes

Mycoplasma

Chlamydia

Other

- Mycobacterium tuberculosis

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Figure 30.16 Antimicrobial spectrum of oxazolidinones.

C. Resistance

Resistance primarily occurs via reduced binding at the target site. Reduced susceptibility and resistance have been reported in Staphylococcus aureus and Enterococcus sp. Cross-resistance with other protein synthesis inhibitors does not occur.

D. Pharmacokinetics

Linezolid and *tedizolid* are well absorbed after oral administration. IV formulations are also available. These drugs distribute widely throughout the body. Although the metabolic pathway of *linezolid* has not been fully determined, it is known that it is metabolized via oxidation to two inactive metabolites. The drug is excreted both by renal and nonrenal routes. *Tedizolid* is metabolized by sulfation. The majority of elimination occurs via the liver, and drug is mainly excreted in the feces. No dose adjustments are required for either agent for renal or hepatic dysfunction.

E. Adverse effects

The most common adverse effects are gastrointestinal upset, nausea, diarrhea, headache, and rash. Thrombocytopenia has been reported, usually in patients taking the drug for longer than 10 days. *Linezolid* and *tedizolid* possess nonselective monoamine oxidase inhibitor activity and may lead to serotonin syndrome if given concomitantly with large quantities of tyramine-containing foods, selective serotonin reuptake inhibitors, or monoamine oxidase inhibitors. The condition is reversible when the drug is discontinued. Irreversible peripheral neuropathies and optic neuritis causing blindness have been associated with greater than 28 days of use, limiting utility for extended-duration treatments.

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IX. LEFAMULIN

Lefamulin [leh-FAM-ewe-lin] is the first antibiotic in the pleuromutilin class and is approved for treatment of community-acquired pneumonia. It works by interacting with the A and P sites on the peptidyl transfer center of the 50s subunit, preventing the binding of tRNA and peptide transfer. *Lefamulin* is bacteriostatic against S. aureus and Streptococcus pyogenes and is bactericidal against S. pneumoniae, Mycoplasma pneumoniae, and H. influenzae. Resistance to *lefamulin* is primarily caused by alterations in the ribosomal binding target. *Lefamulin* is available in both IV and oral formulations and reaches significant concentrations in the epithelial lining fluid of the lungs. *Lefamulin* is primarily metabolized by CYP3A4 and is predominantly excreted in the feces. Due to this metabolism, drugs that strongly induce or inhibit CYP3A4 are contraindicated with *lefamulin.* Gastrointestinal symptoms are the most commonly reported adverse effects. Use of *lefamulin* in pregnancy is not advised.

X. CHLORAMPHENICOL

The use of *chloramphenicol* [klor-am-FEN-i-kole], a broad-spectrum antibiotic, is restricted to life-threatening infections for which no alternatives exist.

A. Mechanism of action

Chloramphenicol binds reversibly to the bacterial 50S ribosomal subunit and inhibits protein synthesis at the peptidyl transferase reaction (Figure 30.2). Because of some similarity of mammalian mitochondrial ribosomes to those of bacteria, protein and ATP synthesis in these organelles may be inhibited at high circulating *chloramphenicol* concentrations, producing bone marrow toxicity. [Note: The oral formulation of *chloramphenicol* was removed from the US market due to this toxicity.]

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B. Antibacterial spectrum

Chloramphenicol is active against many types of microorganisms including chlamydiae, rickettsiae, spirochetes, and anaerobes. The drug is primarily bacteriostatic, but it may exert bactericidal activity depending on the dose and organism.

C. Resistance

Resistance is conferred by the presence of enzymes that inactivate *chloramphenicol.* Other mechanisms include decreased ability to penetrate the organism and ribosomal binding site alterations.

D. Pharmacokinetics

Chloramphenicol is administered intravenously and is widely distributed throughout the body. It reaches therapeutic concentrations in the CSF. *Chloramphenicol* primarily undergoes hepatic metabolism to an inactive glucuronide, which is secreted by the renal tubule and eliminated in the urine. Dose reductions are necessary in patients with liver dysfunction or cirrhosis. *Chloramphenicol* is also secreted into breast milk and should be avoided in breastfeeding mothers.

E. Adverse effects

1. **Anemias:** Patients may experience dose-related anemia, hemolytic anemia (observed in patients with glucose-6-phosphate dehydrogenase deficiency), and aplastic anemia. [Note: Aplastic anemia is independent of dose and may occur after therapy has ceased.]

2. **Gray baby syndrome:** Neonates have a low capacity to glucuronidate the antibiotic, and they have underdeveloped renal function, which decreases their ability to excrete the drug. This leads to drug accumulation to concentrations that interfere with the function of mitochondrial ribosomes, causing poor feeding, depressed breathing, cardiovascular collapse,

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cyanosis (hence the term “gray baby”), and death. Adults who have received very high doses of *chloramphenicol* may also exhibit this toxicity.

3. **Drug interactions:** *Chloramphenicol* inhibits CYP3A4 and CYP2C19, preventing the metabolism of drugs such as *alprazolam*, *warfarin*, and *phenytoin*, which may potentiate their effects.

XI. QUINUPRISTIN/DALFOPRISTIN

Quinupristin/dalfopristin [KWIN-yoo-pris-tin/DAL-foh-pris-tin] is a mixture of two streptogramins in a ratio of 30 to 70, respectively. Due to significant adverse effects, this combination drug is normally reserved for the treatment of severe infections caused by *vancomycin*-resistant Enterococcus faecium (VRE) in the absence of other therapeutic options.

A. Mechanism of action

Each component of this combination drug binds to a separate site on the 50S bacterial ribosome. *Dalfopristin* disrupts elongation by interfering with the addition of new amino acids to the peptide chain. *Quinupristin* prevents elongation similar to the macrolides and causes release of incomplete peptide chains. Thus, they synergistically interrupt protein synthesis. The combination drug has bactericidal activity against most susceptible organisms and has a long PAE.

B. Antibacterial spectrum

Quinupristin/dalfopristin is active primarily against gram-positive cocci, including those resistant to other antibiotics. Its primary use is for the treatment of E. faecium infections, including VRE strains, against which it is bacteriostatic. The drug is not effective against E. faecalis.

C. Resistance

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Enzymatic processes commonly account for resistance to these agents. For example, the presence of a ribosomal enzyme that methylates the target bacterial 23S ribosomal RNA site can interfere in *quinupristin* binding. In some cases, the enzymatic modification can change the action from bactericidal to bacteriostatic. Plasmid-associated acetyltransferase inactivates *dalfopristin.* An active efflux pump can also decrease levels of the antibiotics in bacteria.

D. Pharmacokinetics

Quinupristin/dalfopristin is available intravenously. It does not achieve therapeutic concentrations in CSF. Both compounds undergo hepatic metabolism, with excretion mainly in the feces.

E. Adverse effects

Venous irritation commonly occurs when *quinupristin/dalfopristin* is administered through a peripheral rather than a central line. Hyperbilirubinemia occurs in about 25% of patients, resulting from a competition with the antibiotic for excretion. Arthralgia and myalgia have been reported when higher doses are administered. *Quinupristin/dalfopristin* inhibits CYP3A4, and concomitant administration with drugs that are metabolized by this pathway may lead to toxicities.

Chapter Summary

- Tetracyclines are effective against a wide range of bacteria and can be used to treat infections such as Lyme disease, cholera, and peptic ulcer disease. Tetracyclines are contraindicated in young children and pregnancy due to risk of tooth discoloration.
- Aminoglycosides are available in IV form only (with exception of *neomycin*) and are effective against gram-negative infections. Their primary adverse events include ototoxicity and nephrotoxicity.
- Macrolide antibiotics are effective against a wide range of infections including chlamydial infections, Legionnaires' disease, and Mycobacterium avium complex. The most common adverse effect with macrolides is gastrointestinal upset.

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- *Clindamycin* is a common cause of C. difficile infection, and *fidaxomicin* is an effective treatment against C. difficile.
- *Linezolid* and *tedizolid* are effective mostly against gram-positive bacteria. Both agents are available in IV and oral formulations. Their main adverse events are gastrointestinal in nature and thrombocytopenia when therapy extends past 10 days.
- *Lefamulin* is a pleuromutilin antibiotic that is indicated for community-acquired pneumonia due to high drug concentrations in the lungs.

STUDY QUESTIONS

Choose the ONE best answer.

30.1 Which of the following describes the mechanism of action of tetracycline antibiotics?

A. Bind the 30S subunit of the bacterial ribosome, preventing binding of tRNA to the mRNA–ribosome complex.
B. Bind the 30S ribosomal subunit, interfering with assembly of the functional ribosomal apparatus.
C. Bind irreversibly to a site on the 50S subunit of the bacterial ribosome, inhibiting translocation steps of protein synthesis.
D. Bind the bacterial 23S ribosomal RNA of the 50S subunit, inhibiting the formation of the 70S initiation complex.

Correct answer = A. Tetracyclines enter susceptible organisms via passive diffusion and also by an energy-dependent transport protein mechanism unique to the bacterial inner cytoplasmic membrane. The drugs bind reversibly to the 30S subunit of the bacterial ribosome. This action prevents binding of tRNA to the mRNA–ribosome complex, thereby inhibiting bacterial protein synthesis. B is the mechanism for aminoglycosides, C is the mechanism for macrolides, and D is the mechanism for oxazolidinones.

30.2 Which of the following antibiotic agents should not be given to children less than 8 years of age due to its deposition in bone and teeth?

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A. Azithromycin
B. Doxycycline
C. Linezolid
D. Quinupristin/dalfopristin

Correct answer = B. Tetracyclines are contraindicated in this age group because they are deposited in tissues undergoing calcification, such as teeth and bone, and can stunt growth.

30.3 Aminoglycosides are commonly used for their concentration-dependent bactericidal activity against which of the following group of organisms?

A. Gram-positive aerobes
B. Gram-negative aerobes
C. Gram-positive anaerobes
D. Gram-negative anaerobes

Correct answer = B. Although aminoglycosides (such as gentamicin) are sometimes used synergistically against gram-positive aerobes, this is not their most common use. They are typically used for their activity against gram-negative aerobes. Aminoglycosides do not have good anaerobic activity.

30.4 A 77-year-old woman was started on antibiotics for pneumonia treatment. After 3 days of antibiotic therapy, the serum creatinine doubled. Which of the following antibiotics is most likely responsible for this increase in serum creatinine?

A. Doxycycline
B. Clarithromycin
C. Tobramycin
D. Linezolid

Correct answer = C. Aminoglycosides such as tobramycin accumulate in the proximal tubular cells of the kidney and disrupt calcium-mediated transport processes. This results in kidney damage ranging from mild, reversible renal impairment to severe, potentially irreversible acute tubular necrosis.

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Nephrotoxicity is not commonly associated with tetracyclines (doxycycline), macrolides (clarithromycin), or oxazolidinones (linezolid).

30.5 A 24-year-old pregnant woman was diagnosed with community-acquired pneumonia and will be managed in the outpatient setting. Which of the following antibiotics is a safe option for this patient to treat her pneumonia?

A. Azithromycin
B. Doxycycline
C. Fidaxomicin
D. Gentamicin

Correct answer = A. Azithromycin is available orally and considered safe in pregnancy. Doxycycline should not be used in pregnancy due to its ability to cross the placenta and affect bone and skeletal development in the fetus. Fidaxomicin does not reach therapeutic concentrations in serum or at this site of infection. It concentrates in the gut. Gentamicin crosses the placental barrier and may accumulate in fetal plasma and amniotic fluid. It would also not be used clinically in this outpatient scenario.

30.6 A patient is diagnosed with Clostridioides difficile–associated diarrhea. Which of the following antibiotics is the best choice for this infection?

A. Azithromycin
B. Clindamycin
C. Fidaxomicin
D. Tobramycin

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Correct answer = C. Fidaxomicin is the only protein synthesis inhibitor antibiotic that is effective against Clostridioides difficile diarrhea.

30.7 Linezolid would be a good choice for antibiotic treatment in which of the following patient scenarios?

A. Bacteremia caused by Staphylococcus aureus

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B. Urinary tract infection caused by Escherichia coli
C. Pneumonia caused by drug-resistant Streptococcus pneumoniae
D. Diabetic foot infection caused by Pseudomonas aeruginosa

Correct answer = C. Linezolid does have coverage against resistant S. pneumoniae. It is not an optimal choice for the treatment of bacteremia. Linezolid also does not have gram-negative coverage against E. coli and P. aeruginosa.

30.8 A patient has an infection with culture results showing growth of MRSA, VRE, and extended-spectrum β-lactamase–producing E. coli. Which of the following antibiotics would be effective against all three bacteria?

A. Clarithromycin
B. Linezolid
C. Quinupristin/dalfopristin
D. Tigecycline

Correct answer = D. Tigecycline is active against MRSA, VRE, and ESBL-producing bacteria. Clarithromycin is not active against MRSA. Linezolid and quinupristin/dalfopristin are only active against gram-positive bacteria.

30.9 A patient has pneumonia that is requiring treatment. They are receiving a selective serotonin reuptake inhibitor for treatment of depression. Which of the following antibiotics is contraindicated in this patient?

A. Doxycycline
B. Gentamicin
C. Linezolid
D. Azithromycin

Correct answer = C. Due to the risk of serotonin syndrome, linezolid use is contraindicated in patients taking selective serotonin reuptake inhibitors.

@Pharmacy_Z

30.10 Which of the following antibiotics is contraindicated in a patient who is currently receiving a strong CYP3A4 inhibitor?

A. Minocycline
B. Lefamulin
C. Plazomicin
D. Fidaxomicin

Correct answer = B. Due to being metabolized by CYP3A4, concomitant use of lefamulin and strong CYP3A4 inhibitors or inducers is contraindicated.

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31

Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics

John M. Allen, Jacinda C. Abdul-Mutakabbir

I. FLUOROQUINOLONES

Discovery of quinolone antimicrobials led to the development of numerous compounds utilized in clinical practice. Following synthesis of *nalidixic acid* in the early 1960s, continued modification of the quinolone nucleus expanded the spectrum of activity, improved pharmacokinetics, and stabilized compounds against common mechanisms of resistance. Due to these enhancements, quinolone antimicrobials were rapidly integrated into human and agricultural medicine. Unfortunately, overuse resulted in rising rates of resistance in gram-negative and gram-positive organisms, increased frequency of Clostridioides difficile infections, and identification of numerous untoward adverse effects. Consequently, these agents have been relegated to second-line options for various indications. This chapter reviews key characteristics of fluoroquinolones and their role in therapy. The fluoroquinolones and other antibiotics discussed in this chapter are listed in Figure 31.1.

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FLUOROQUINOLONES

Ciprofloxacin CIPRO
Delafloxacin BAXDELA
Gemifloxacin FACTIVE
Levofloxacin GENERIC ONLY
Moxifloxacin AVELOX, MOXEZA, VIGAMOX
Ofloxacin GENERIC ONLY

INHIBITORS OF FOLATE SYNTHESIS

Mafenide SULFAMYLON
Silver sulfadiazine SILVADENE, SSD, THERMAZENE
Sulfadiazine GENERIC ONLY
Sulfasalazine AZULFIDINE

INHIBITORS OF FOLATE REDUCTION

Pyrimethamine DARAPRIM
Trimethoprim GENERIC ONLY

COMBINATION OF INHIBITORS OF FOLATE SYNTHESIS AND REDUCTION

Cotrimoxazole (trimethoprim + sulfamethoxazole) BACTRIM, SEPTRA

URINARY TRACT ANTISEPTICS

Methenamine HIPREX, UREX
Nitrofurantoin MACROBID, MACRODANTIN

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Figure 31.1 Summary of drugs described in this chapter.

A. Mechanism of action

Most bacterial species maintain two distinct type II topoisomerases that assist with deoxyribonucleic acid (DNA) replication—DNA gyrase and topoisomerase IV. DNA gyrase is responsible for reducing torsional stress ahead of replicating forks by breaking double-strand DNA and introducing negative supercoils. Topoisomerase IV assists in separating daughter chromosomes once replication is completed. Following cell wall entry through porin channels, fluoroquinolones bind to these enzymes and interfere with DNA ligation. This interference increases the number of permanent chromosomal breaks, triggering cell lysis. In general, fluoroquinolones have different targets for gram-negative (DNA gyrase) and gram-positive organisms (topoisomerase IV), resulting in rapid cell death.

B. Antimicrobial spectrum

Fluoroquinolones are bactericidal and exhibit area under the curve/minimum inhibitory concentration–dependent killing. A major facet of their development centered on improving microbiologic coverage. Modifications to the quinolone nucleus steadily improved topoisomerase inhibitory activity and facilitated bacterial cell wall penetration. These changes enhanced activity against a variety of pathogens including aerobic gram-negative and gram-positive organisms, atypical organisms (for example, Chlamydia spp., Legionella spp., and Mycoplasma spp.), and anaerobes. Based on the impact of these structural changes, fluoroquinolones are often classified according to spectrum of activity.

First-generation compounds (for example, *nalidixic acid*) were narrow-spectrum agents with activity against aerobic gram-negative bacilli, mostly *Enterobacteriaceae.* Second-generation

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compounds (for example, *ciprofloxacin*) exhibit improved intracellular penetration and broadened coverage, which includes *Enterobacteriaceae*, Pseudomonas aeruginosa, Haemophilus influenzae, Neisseria spp., Chlamydia spp., and Legionella spp. Third-generation compounds (for example, *levofloxacin*) maintain the bacterial spectrum of second-generation agents, with improved activity against Streptococcus spp., including S. pneumoniae, *methicillin*-susceptible Staphylococcus aureus, Stenotrophomonas maltophilia, and *Mycobacterium* spp. Fourth-generation compounds (*moxifloxacin*, *gemifloxacin*, and *delafloxacin*) have enhanced gram-positive activity, including Staphylococcus and Streptococcus spp. *Delafloxacin* has activity against *methicillin*-resistant Staphylococcus aureus (MRSA) and Enterococcus faecalis. Further, *delafloxacin* and *moxifloxacin* have activity against Bacteroides fragilis and Prevotella spp., while maintaining activity against *Enterobacteriaceae* and H. influenzae. From this group, only *delafloxacin* has activity against P. aeruginosa. Lastly, these agents maintain atypical coverage, with *moxifloxacin* and *delafloxacin* showing activity against Mycobacteria spp. Common therapeutic applications of fluoroquinolones are shown in Figure 31.2.

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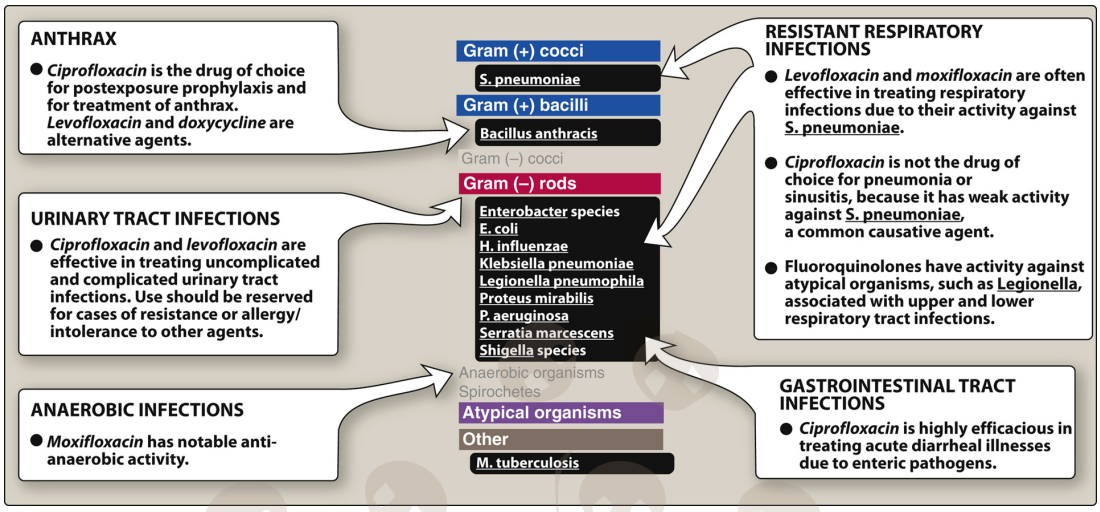

Figure 31.2 Typical therapeutic applications of fluoroquinolones.

C. Resistance

Numerous mechanisms of fluoroquinolone resistance exist in clinical pathogens. High-level fluoroquinolone resistance is primarily driven by chromosomal mutations within topoisomerases, although decreased entry, efflux systems, and modifying enzymes play a role. Mechanisms responsible for resistance include the following:

1. **Altered target binding:** Mutations in bacterial genes encoding DNA gyrase or topoisomerase IV (for example, gyrA or parC) alter target site structure and reduce binding efficiency of fluoroquinolones.

2. **Decreased accumulation:** Reduced intracellular concentration is linked to (1) a reduction in membrane permeability or (2) efflux pumps. Alterations in membrane permeability are mediated through a reduction in outer membrane porin proteins, thus limiting drug access to topoisomerases. Efflux pumps actively remove fluoroquinolones from the cell.

3. **Fluoroquinolone degradation:** An aminoglycoside acetyltransferase variant can acetylate fluoroquinolones,

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rendering them inactive.

D. Pharmacokinetics

1. Absorption: Fluoroquinolones are well absorbed after oral administration, with *levofloxacin* and *moxifloxacin* having a bioavailability that exceeds 90% (Figure 31.3). Ingestion of fluoroquinolones with *sucralfate*, aluminum- or magnesium-containing antacids, or dietary supplements containing iron or zinc can reduce the absorption. Calcium and other divalent cations also interfere with the absorption of these agents (Figure 31.4).

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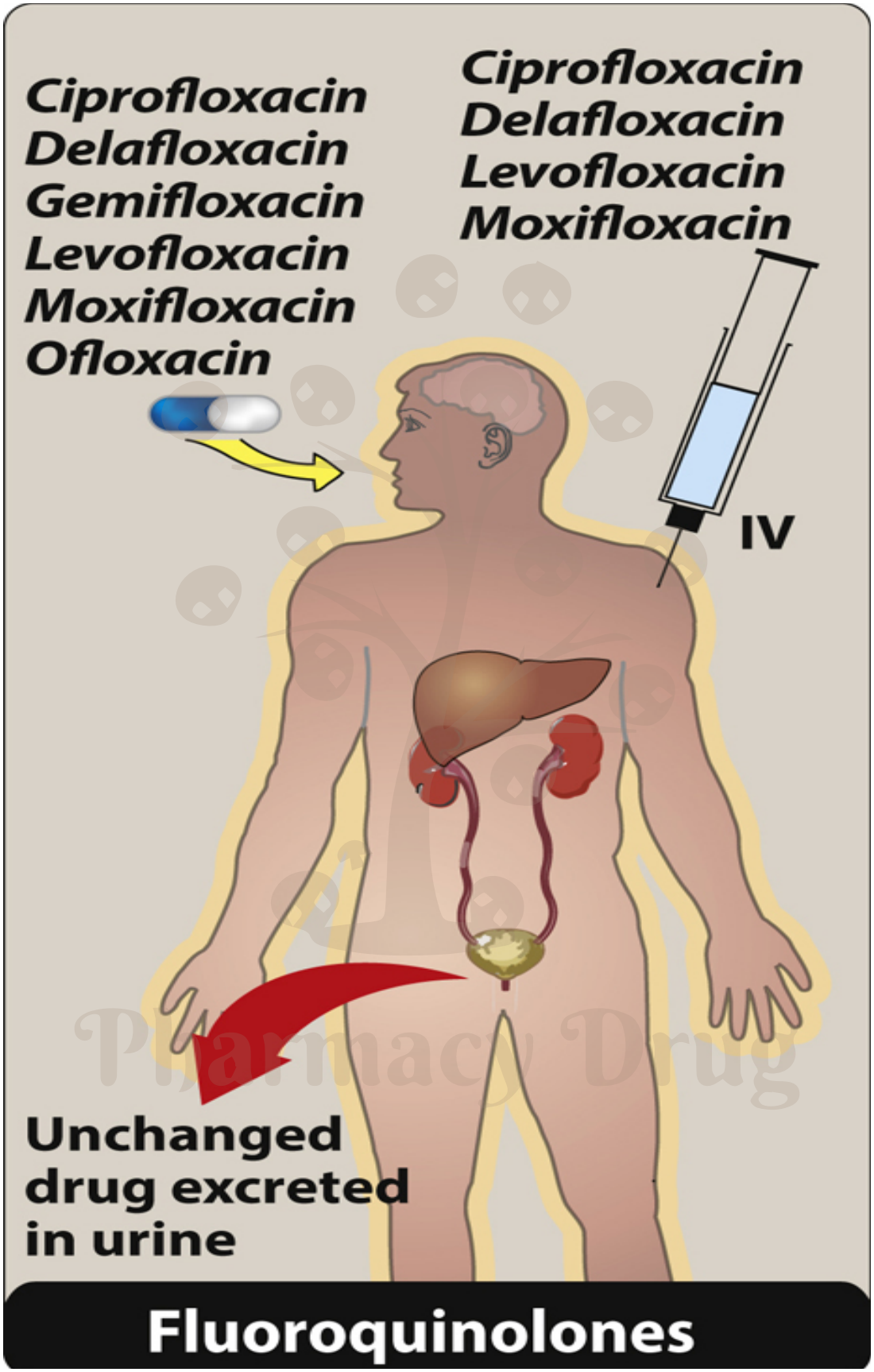

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Figure 31.3 Administration and fate of the fluoroquinolones.

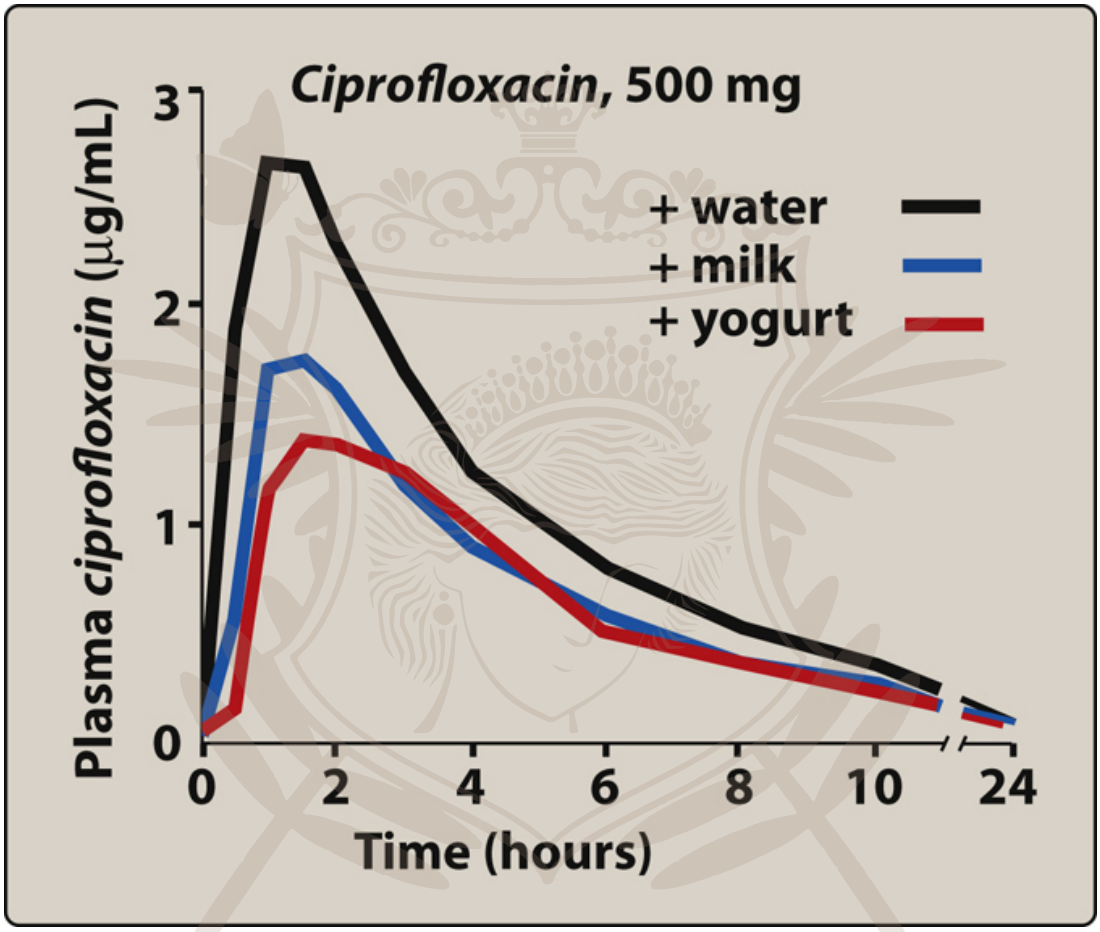

Figure 31.4 Effect of dietary calcium on the absorption of *ciprofloxacin*.

2. Distribution: Binding to plasma proteins ranges from 20% to 84%. Fluoroquinolones distribute well into all tissues and body fluids. Concentrations are high in the bone, urine (except *moxifloxacin*), kidney, prostatic tissue (but not prostatic fluid), and lungs as compared to serum. Penetration into cerebrospinal fluid is good, and these agents may be considered in certain central nervous system (CNS) infections. Accumulation in macrophages and polymorphonuclear

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leukocytes results in activity against intracellular organisms such as Listeria, Chlamydia, and Mycobacterium.

3. Elimination: Most fluoroquinolones are excreted renally. Therefore, dosage adjustments are needed in renal dysfunction. *Moxifloxacin* is metabolized primarily by the liver, and while there is some renal excretion, no dose adjustment is required for renal impairment (Figure 31.3).

E. Adverse reactions

In general, fluoroquinolones are well tolerated (Figure 31.5). Common adverse effects leading to discontinuation are nausea, vomiting, headache, and dizziness. These agents carry boxed warnings for tendinitis, tendon rupture, peripheral neuropathy, and CNS effects (hallucinations, anxiety, insomnia, confusion, and seizures). Patients taking fluoroquinolones are at risk for phototoxicity resulting in exaggerated sunburn reactions. Patients should use sunscreen and avoid excessive exposure to ultraviolet (UV) light. Arthropathy is uncommon, but arthralgia and arthritis are reported with fluoroquinolone use in pediatric patients. Use in the pediatric population should be limited to distinct clinical scenarios (for example, cystic fibrosis exacerbation). Hepatotoxicity or blood glucose disturbances (usually in patients with diabetes receiving oral hypoglycemic agents or insulin) have been observed. Identification of any of these events should result in prompt removal of the agent. Fluoroquinolones may prolong the QT_c interval, and these agents should be avoided in patients predisposed to arrhythmias or taking medication associated with QT prolongation. *Ciprofloxacin* inhibits CYP1A2-mediated metabolism and may inhibit CYP3A4-mediated metabolism. Serum concentrations of medications such as *alprazolam*, *tizanidine*, *warfarin*, *ropinirole*, *duloxetine*, *caffeine*, *sildenafil*, and *zolpidem* may be increased (Figure 31.6).

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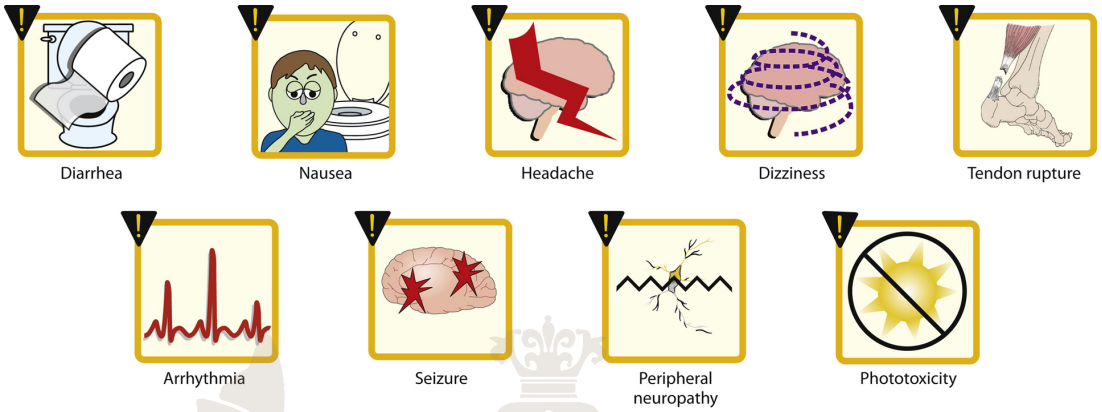

Figure 31.5 Some adverse reactions to fluoroquinolones.

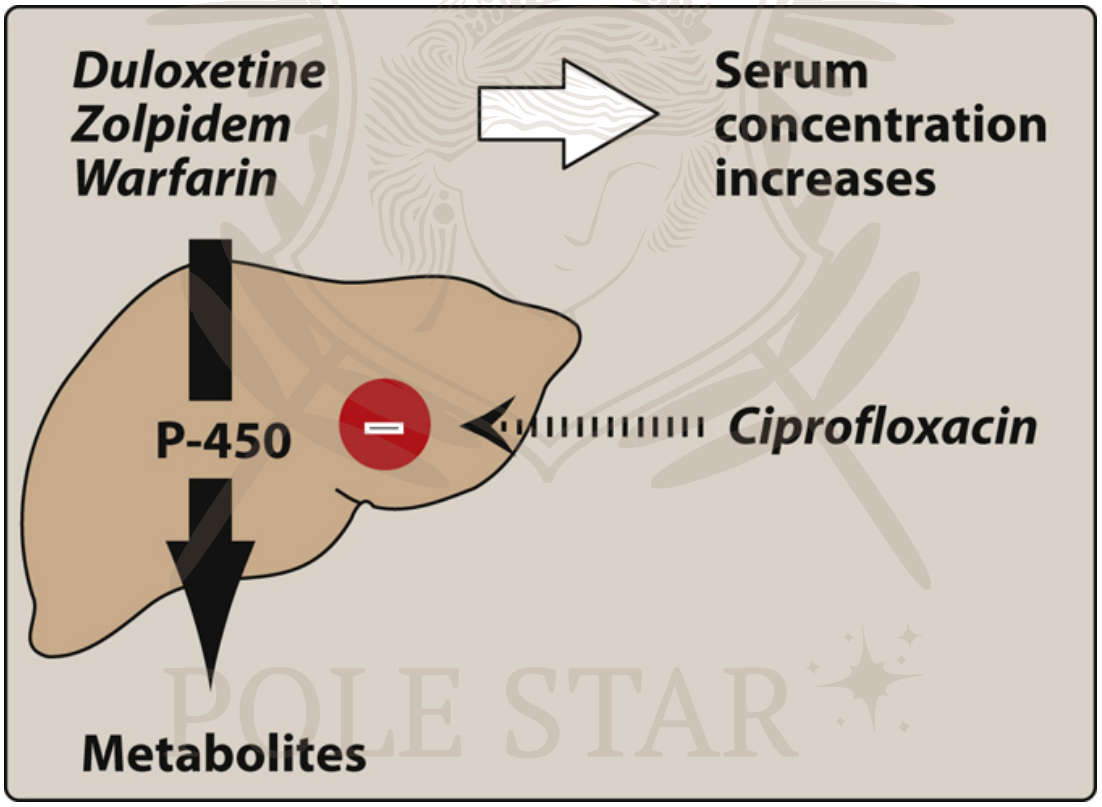

Figure 31.6 Drug interactions with *ciprofloxacin*.

F. Examples of clinically useful fluoroquinolones

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Due to increasing resistance and boxed warnings, fluoroquinolones should be used with caution in select circumstances. They may be considered in patients who do not tolerate other agents (for example, severe β-lactam allergies) or as definitive therapy once susceptibilities are available. Listed below are potential indications for these agents. [Note: In addition to the indications below, *levofloxacin*, *moxifloxacin*, and *gatifloxacin* are available in topical ophthalmic preparations for the treatment of bacterial conjunctivitis.]

1. Ciprofloxacin: *Ciprofloxacin* [SIP-roe-FLOX-a-sin] has good activity against gram-negative bacilli, including P. aeruginosa. *Ciprofloxacin* is used in the treatment of traveler's diarrhea, typhoid fever, and anthrax. It is a second-line agent for infections arising from intra-abdominal, lung, skin, or urine sources. Of note, high-dose therapy should be employed when treating Pseudomonas infections.

2. Levofloxacin: *Levofloxacin* [leev-oh-FLOX-a-sin] has similar activity to *ciprofloxacin* and they are often interchanged when managing gram-negative bacilli, including P. aeruginosa. *Levofloxacin* has enhanced activity against S. pneumoniae and is first-line therapy for community-acquired pneumonia (CAP). It is a second-line agent for the treatment of S. maltophilia.

3. Moxifloxacin: *Moxifloxacin* [mox-ee-FLOX-a-sin] has enhanced activity against gram-positive organisms (for example, S. pneumoniae), gram-negative anaerobes, and Mycobacterium spp. The drug may be used for CAP, but not hospital-acquired pneumonia due to poor coverage of P. aeruginosa. It may be considered for mild- to moderate intra-abdominal infections, but should be avoided if patients have fluoroquinolone exposure within the previous 3 months due to increasing B. fragilis resistance. *Moxifloxacin* may be considered as a second-line agent for management of drug-susceptible tuberculosis.

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4.Gemifloxacin: *Gemifloxacin* [gem-ee-FLOX-a-sin] is indicated for the management of community-acquired respiratory infections. Unlike the other compounds, it is only available as an oral formulation.

5.Delafloxacin: *Delafloxacin* [del-a-FLOX-a-sin] has improved activity against gram-positive cocci, including MRSA and Enterococcus spp. Due to its spectrum of activity, it is an option for managing acute bacterial skin and skin structure infections, and CAP. It is available as an intravenous and oral formulation.

II. FOLATE ANTAGONISTS

Folic acid is a coenzyme essential in the synthesis of ribonucleic acid (RNA), DNA, and certain amino acids. In the absence of folate, cells cannot grow or divide. Humans use dietary folate to synthesize the critical folate derivative, tetrahydrofolic acid. By contrast, many bacteria are impermeable to folate derivatives and rely on their ability to synthesize folate de novo (Figure 31.7). Sulfonamides (sulfa drugs) are a family of antibiotics that inhibit de novo synthesis of folate. A second type of folate antagonist, *trimethoprim*, prevents microorganisms from converting dihydrofolic acid to tetrahydrofolic acid. Thus, both sulfonamides and *trimethoprim* interfere with the ability of an infecting bacterium to perform DNA synthesis and other essential cellular functions. The combination of the sulfonamide *sulfamethoxazole* with *trimethoprim* (TMP/SMX) provides a synergistic effect or increased bacteriostatic activity due to the duality in the mechanisms of action.

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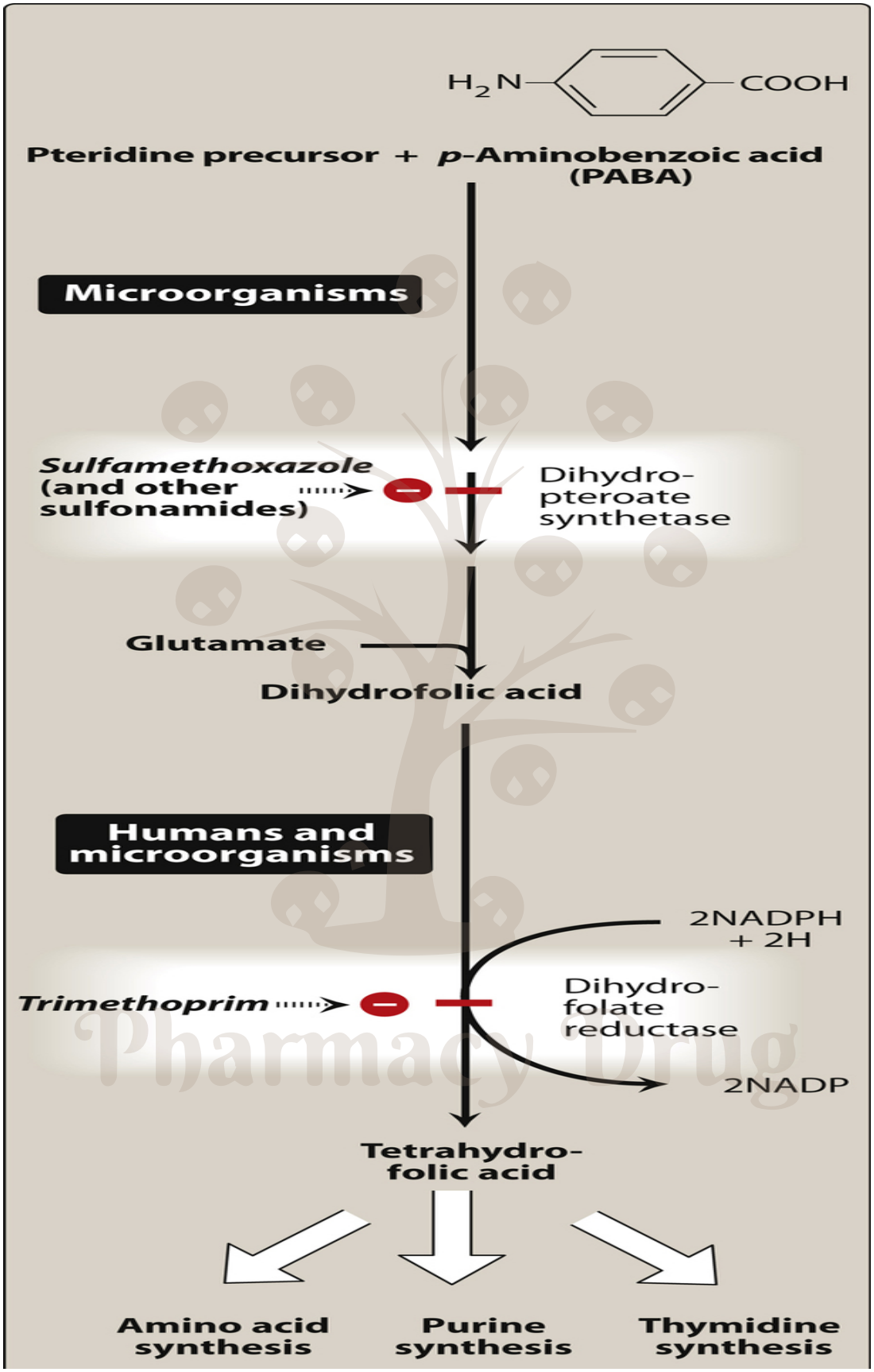

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Figure 31.7 Inhibition of tetrahydrofolate synthesis by sulfonamides and *trimethoprim*.

III. SULFONAMIDES

Sulfonamides (sulfa) drugs were among the first antibiotics used in clinical practice. Today, they are seldom prescribed alone except in developing countries, where they are employed because of low cost and efficacy.

A. Mechanism of action

Microorganisms use the enzyme dihydropteroate synthetase to create dihydrofolic acid from the precursor molecule *p*-aminobenzoic acid (PABA). Sulfonamides are synthetic analogs of PABA. Because of their structural similarity, sulfonamides compete with PABA to inhibit dihydropteroate synthetase and ultimately inhibit the genesis of bacterial dihydrofolic acid (Figure 31.7). Thus, dihydrofolic acid ceases to be converted to the critical derivative, tetrahydrofolic acid. These agents, including *TMP/SMX*, are bacteriostatic, preventing continued bacterial growth rather than killing the bacteria (bactericidal).

B. Antibacterial spectrum

Sulfa drugs have in vitro activity against gram-negative and gram-positive organisms. Common organisms include *Enterobacteriaceae* (Escherichia coli, Klebsiella pneumoniae, Enterobacter spp.), H. influenzae, Streptococcus spp., Staphylococcus spp., and Nocardia. Additionally, *sulfadiazine* [sul-fa-DYE-a-zeen], a sulfa antibiotic, in combination with the dihydrofolate reductase inhibitor *pyrimethamine* [py-ri-METH-a-meen] is the preferred treatment for toxoplasmosis.

C. Resistance

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Bacteria that obtain folate from their environment are naturally resistant to sulfa drugs. Acquired bacterial resistance to the sulfa drugs can arise from plasmid transfers or random mutations. Resistance may be due to (1) altered dihydropteroate synthetase, (2) decreased cellular permeability to sulfa drugs, or (3) enhanced production of the natural substrate, PABA. [Note: Organisms resistant to one member of this drug family are resistant to all.]

D. Pharmacokinetics

1. Absorption: Most sulfa drugs are well absorbed following oral administration (Figure 31.8). An exception is *sulfasalazine* [sul-fa-SAL-a-zeen]. It is not absorbed when administered orally or as a suppository and, therefore, is reserved for the treatment of chronic inflammatory bowel diseases. [Note: Intestinal flora split *sulfasalazine* into sulfapyridine and 5-aminosalicylate, with the latter exerting the anti-inflammatory effect. Absorption of sulfapyridine can lead to toxicity in patients who are slow acetylators.] Intravenous sulfonamides are generally reserved for patients who are unable to take oral preparations or have severe infections. Because of the risk of sensitization, sulfa drugs are not usually applied topically. However, in burn units, *silver sulfadiazine* [sul-fa-DYE-ah-zeen] or *mafenide* [mah-FEN-ide] *acetate* (α-amino-*p*-toluenesulfonamide) creams have been effective in reducing burn-associated sepsis because they prevent colonization of bacteria. [Note: *Silver sulfadiazine* is preferred because *mafenide* produces pain on application and its absorption may contribute to acid–base disturbances.]

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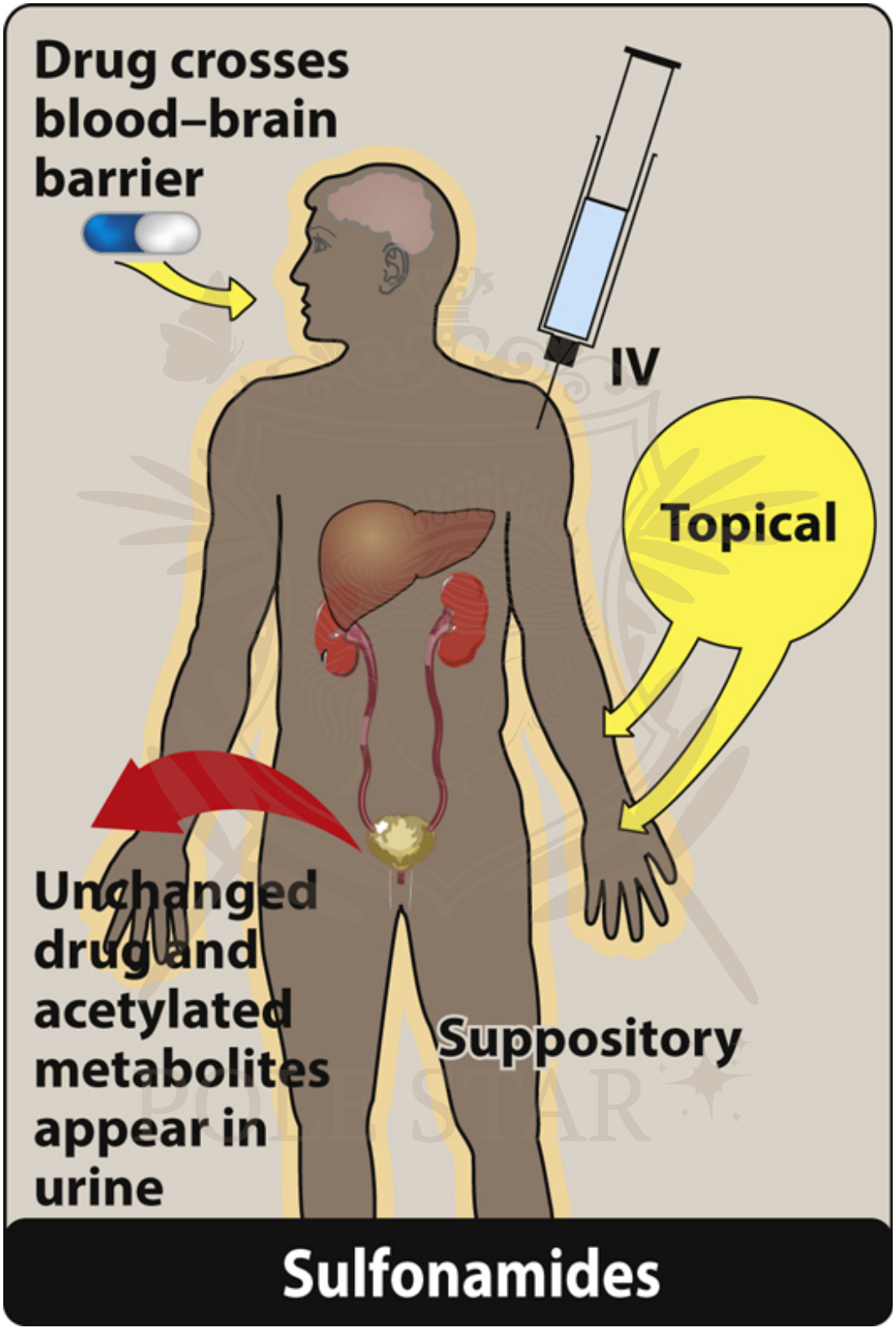

Figure 31.8 Administration and fate of the sulfonamides.

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2.Distribution: Sulfa drugs are bound to serum albumin in circulation and widely distribute throughout body tissues. Sulfa drugs penetrate well into cerebrospinal fluid (even in the absence of inflammation) and cross the placental barrier to enter fetal tissues.

3.Metabolism: Sulfa drugs are acetylated and conjugated primarily in the liver. The acetylated product is devoid of antimicrobial activity but retains the toxic potential to precipitate at neutral or acidic pH. This causes crystalluria ("stone formation"; see below) and potential damage to the kidney.

4.Excretion: Unchanged sulfa drug and metabolites are eliminated via glomerular filtration and secretion, requiring dose adjustments with renal impairment. Sulfonamides may be eliminated in breast milk.

E. Adverse effects

1.Crystalluria: Nephrotoxicity may develop as a result of crystalluria (Figure 31.9). Adequate hydration and alkalinization of urine can prevent the problem by reducing the concentration of drug and promoting its ionization.

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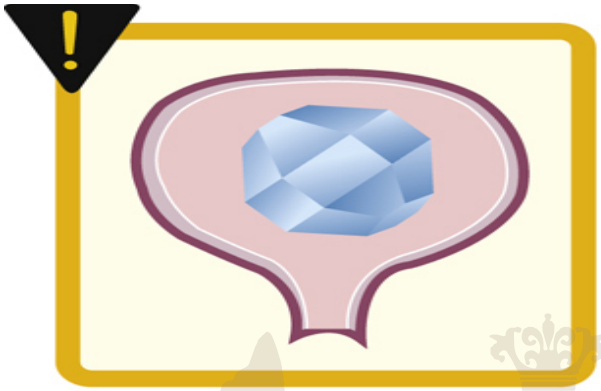
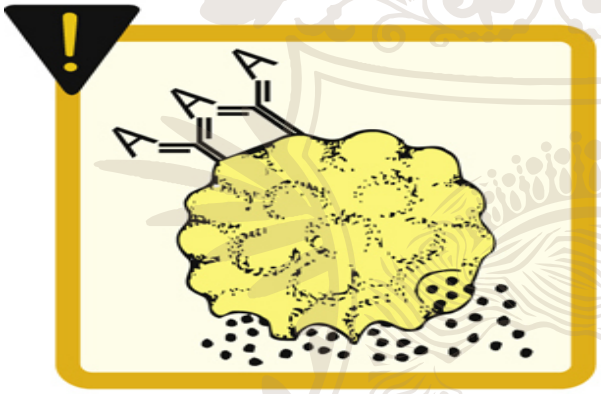
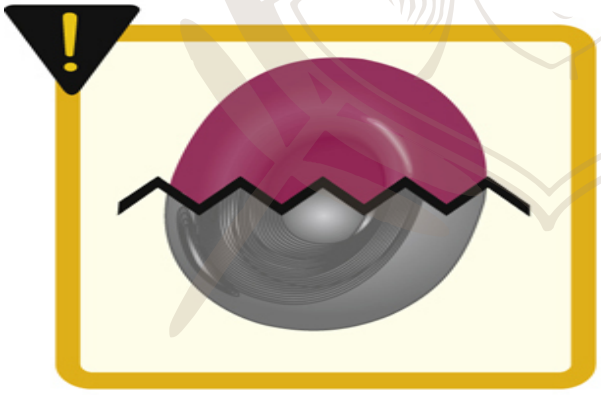


Crystalluria



Hypersensitivity



Hemolytic anemia

Kernicterus

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Figure 31.9 Some adverse reactions to sulfonamides.

2.Hypersensitivity: Hypersensitivity reactions, such as rashes, angioedema, or Stevens–Johnson syndrome, may occur. When patients report previous sulfa allergies, it is paramount to acquire a description of the reaction to direct appropriate therapy. Sulfa drugs are also associated with photosensitivity, and patients should be advised to wear sunscreen and limit sun exposure.

3.Hematopoietic disturbances: Hemolytic anemia is encountered in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Granulocytopenia and thrombocytopenia can also occur. Fatal reactions have been reported from associated agranulocytosis, aplastic anemia, and other blood dyscrasias.

4.Kernicterus: Bilirubin-associated brain damage (kernicterus) may occur in newborns, because sulfa drugs displace bilirubin from binding sites on serum albumin. The bilirubin is then free to pass into the CNS, because the blood–brain barrier is not fully developed.

5.Drug potentiation: *Sulfamethoxazole* potentiates the anticoagulant effect of *warfarin* due to inhibition of CYP2C9, resulting in reduced clearance of *warfarin.* Sulfonamides may also displace *warfarin* from binding sites on serum albumin. Serum *methotrexate* levels may rise through sulfonamide-mediated protein binding displacement. Other CYP2C9 substrates, such as *phenytoin*, may have increased concentrations when given with sulfonamides.

6.Contraindications: Due to the danger of kernicterus, sulfa drugs should be avoided in newborns and infants less than 2 months of age, as well as in pregnant women at term. Sulfonamides should not be given to patients receiving

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methenamine, since they can crystallize in the presence of the acidic urine produced by *methenamine* salts.

IV. TRIMETHOPRIM

Trimethoprim [try-METH-oh-prim], a folate antagonist, was initially available in combination with the sulfonamide *sulfamethoxazole* [sul-fa-meth-OX-a-zole] and later approved for use as a single agent. Today, *trimethoprim* is most commonly used in combination with *sulfamethoxazole* (commonly referred to as *TMP/SMX*).

A. Mechanism of action

Trimethoprim is a potent inhibitor of bacterial dihydrofolate reductase (Figure 31.7). Inhibition of this enzyme prevents the formation of the metabolically active form of folic acid, tetrahydrofolic acid, and thus interferes with normal bacterial cell functions. *Trimethoprim* binds to bacterial dihydrofolate reductase more readily than it does to human dihydrofolate reductase, which accounts for the selective activity and toxicity of the drug.

B. Antibacterial spectrum

The antibacterial spectrum of *trimethoprim* is similar to that of *sulfamethoxazole.* However, *trimethoprim* is 20- to 50-fold more potent than the sulfonamides. *Trimethoprim* may be used alone in the treatment of urinary tract infections (UTIs) and in the treatment of bacterial prostatitis (although fluoroquinolones and *TMP/SMX* are preferred).

C. Resistance

Resistance in gram-negative bacteria is due to the presence of an altered dihydrofolate reductase that has a lower affinity for *trimethoprim.* Efflux pumps and decreased permeability to the drug may play a role in resistance to *trimethoprim*.

D. Pharmacokinetics

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Trimethoprim is rapidly absorbed following oral administration. Because the drug is a weak base, higher concentrations of *trimethoprim* are achieved in the relatively acidic prostatic and vaginal fluids. The drug is widely distributed into body tissues and fluids, including penetration into the cerebrospinal fluid. *Trimethoprim* undergoes some O-demethylation in the liver, but 60% to 80% is renally excreted unchanged.

E. Adverse effects

Trimethoprim can produce the effects of folic acid deficiency. These effects include megaloblastic anemia, leukopenia, and granulocytopenia, especially in pregnant patients and those with nutrient-poor diets. These blood disorders may be reversed by simultaneous administration of *folinic acid* (also known as *leucovorin*), which does not enter bacteria. *Trimethoprim* has a potassium-sparing effect and may cause hyperkalemia, especially at higher doses and when administered with other medication that causes hyperkalemia (for example, angiotensin-converting enzyme inhibitors).

V. TRIMETHOPRIM/SULFAMETHOXAZOLE

The combination of *trimethoprim* with *sulfamethoxazole*, also called *co-trimoxazole* [co-try-MOX-a-zole], shows greater antimicrobial activity than equivalent quantities of either drug used alone (Figure 31.10). The combination was selected because of the synergistic activity and the similarity in the half-lives of the two drugs.

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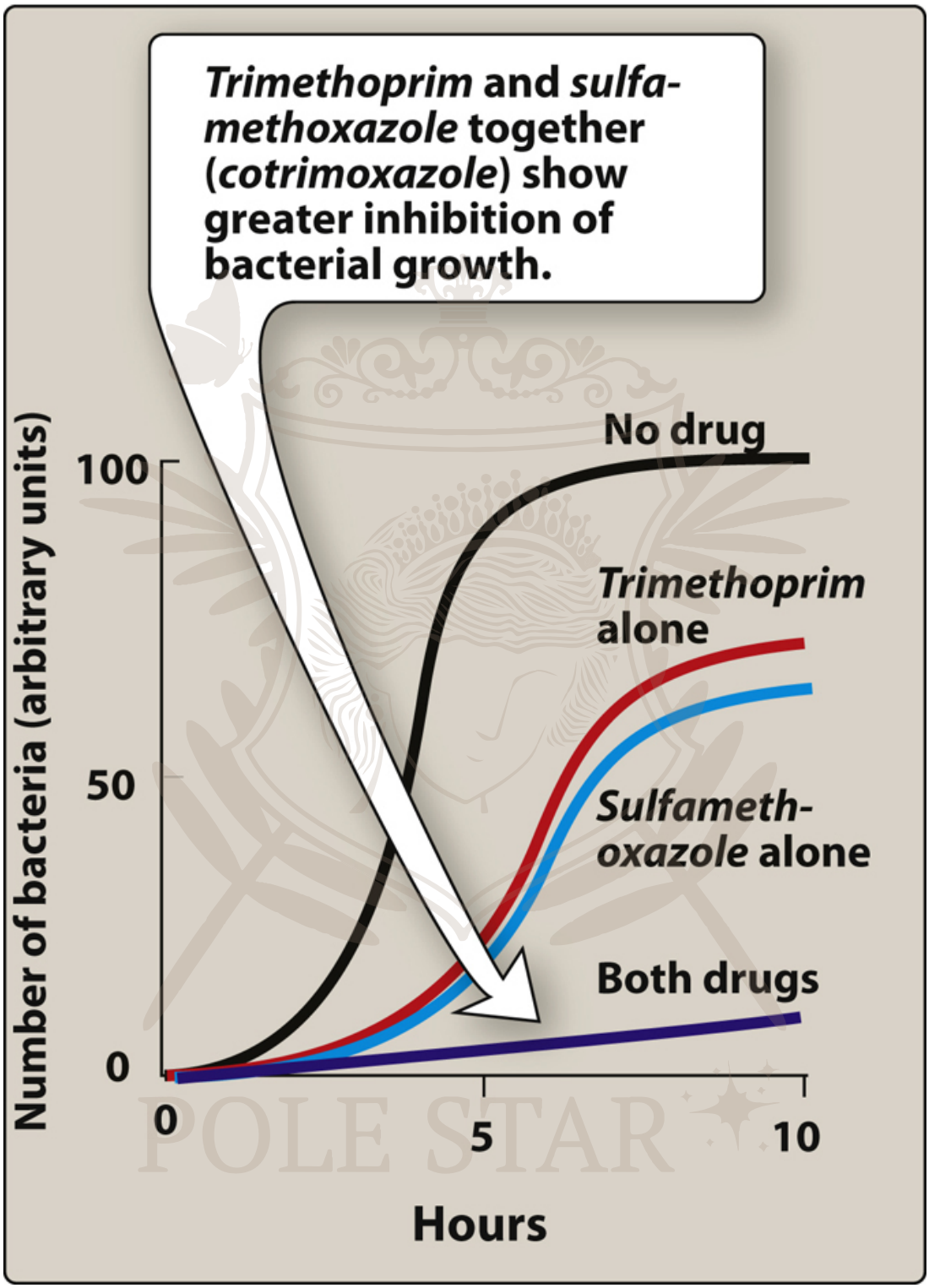

Figure 31.10 Synergism between *trimethoprim* and *sulfamethoxazole* inhibits growth of *Escherichia coli*.

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A. Mechanism of action

The synergistic antimicrobial activity of *TMP/SMX* results from its inhibition of two sequential steps in the synthesis of tetrahydrofolic acid. *Sulfamethoxazole* inhibits the incorporation of PABA into dihydrofolic acid precursors, and *trimethoprim* prevents reduction of dihydrofolate to tetrahydrofolate (Figure 31.7).

B. Antibacterial spectrum

Trimethoprim–sulfamethoxazole has a broader spectrum of antibacterial action than the sulfa drugs alone (Figure 31.11). It is effective in treating UTIs and respiratory tract infections, as well as Pneumocystis jirovecii, toxoplasmosis, Listeria monocytogenes, and Salmonella infections. It has activity against *methicillin*-resistant *S. aureus* and can be particularly useful for skin and soft tissue infections caused by this organism. It is the drug of choice for infections caused by susceptible *Nocardia* spp. and *S. maltophilia.*

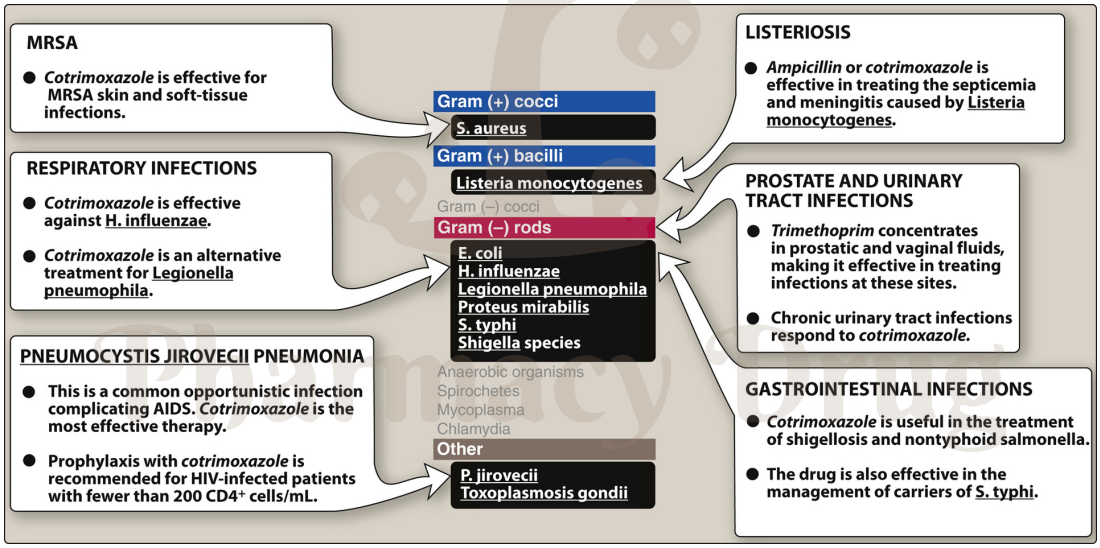

Figure 31.11 Typical therapeutic applications of *sulfamethoxazole* and *trimethoprim* (*cotrimoxazole* or *TMP/SMX*).

A L G r a w a n y

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C. Resistance

Resistance to the *trimethoprim–sulfamethoxazole* combination is encountered less frequently than resistance to either of the drugs alone, because it requires bacterium to maintain simultaneous resistance to both drugs. Nevertheless, significant resistance has been documented in a number of clinically relevant organisms, including *E. coli*.

D. Pharmacokinetics

Trimethoprim–sulfamethoxazole is generally administered orally (Figure 31.12). Intravenous administration may be utilized in patients with severe pneumonia caused by P. jirovecii. Both agents distribute throughout the body. *Trimethoprim* concentrates in the relatively acidic milieu of prostatic fluids, and this accounts for the use of *trimethoprim–sulfamethoxazole* in the treatment of prostatitis. *Trimethoprim–sulfamethoxazole* readily crosses the blood–brain barrier. Both parent drugs and their metabolites are excreted in the urine.

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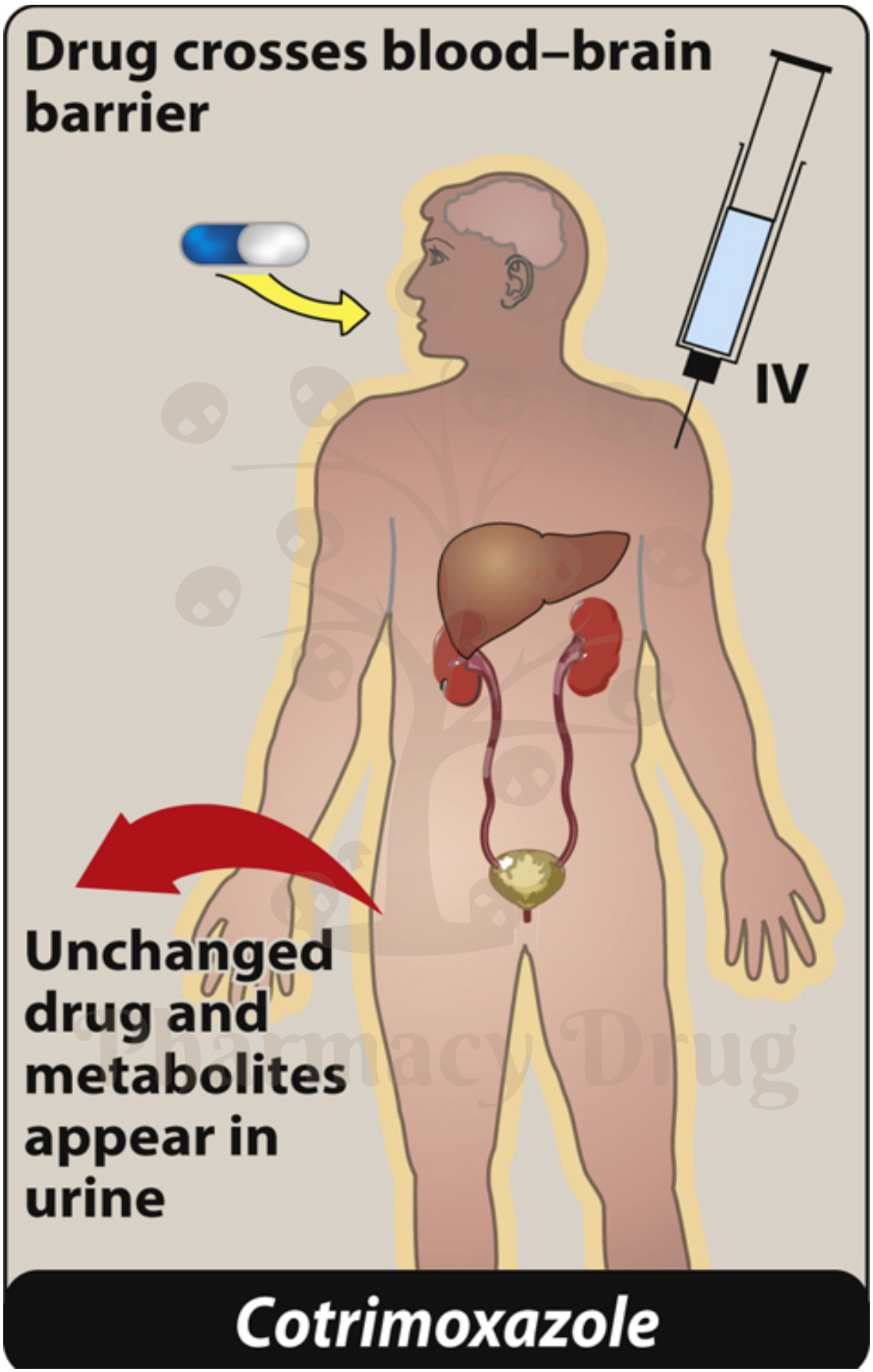

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Figure 31.12 Administration and fate of *sulfamethoxazole* and *trimethoprim* (*TMP/SMX*).

E. Adverse effects

Adverse reactions and drug interactions related to *TMP/SMX* are similar to those expected with each of the individual components, *sulfamethoxazole* and *trimethoprim* (Figure 31.13). The most common adverse reactions are nausea and vomiting, skin rash, hematologic toxicity, and hyperkalemia.

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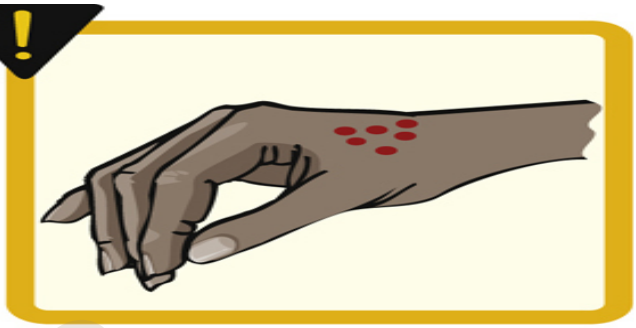
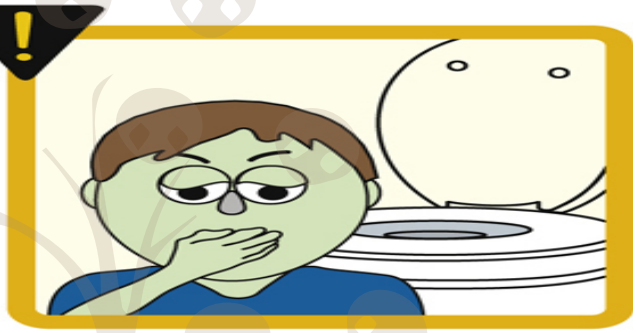
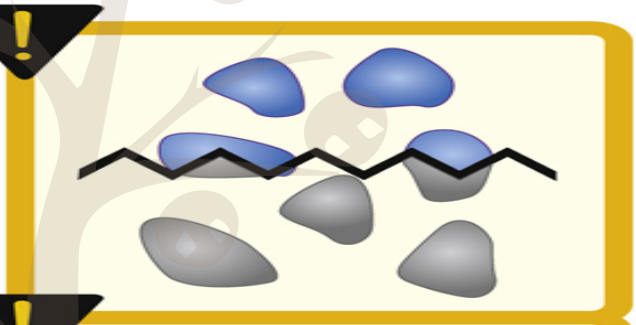
Skin rash

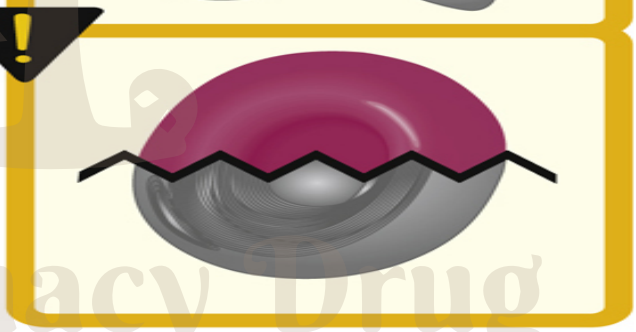


Nausea



Hematologic toxicities





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Hyperkalemia

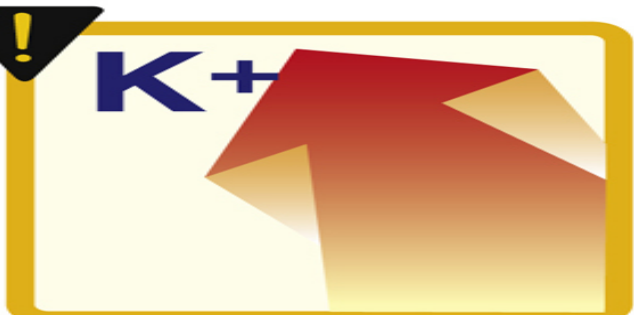

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Figure 31.13 Some adverse reactions to *TMP/SMX*.

VI. URINARY TRACT ANTISEPTICS/ANTIMICROBIALS

UTIs are one of the most common bacterial infections in the world, primarily impacting women and the elderly. Historically, fluoroquinolones and *TMP/SMX* have been first-line therapy for the treatment of UTIs. Unfortunately, resistance has increased among common pathogens (for example, *E. coli*). As a result, *methenamine*, *nitrofurantoin*, and *fosfomycin* (see Chapter 29) can be considered for the treatment or suppression of recurrence, due to their efficacy against common pathogens and high concentrations in the urine.

A. Methenamine

1. Mechanism of action: *Methenamine* [meth-EN-a-meen] salts are hydrolyzed to ammonia and formaldehyde in acidic urine (pH ≤ 5.5). Formaldehyde denatures proteins and nucleic acids, resulting in bacterial cell death. *Methenamine* is combined with a weak acid (for example, hippuric or mandelic acid) to maintain urine acidity and promote production of formaldehyde (Figure 31.14).

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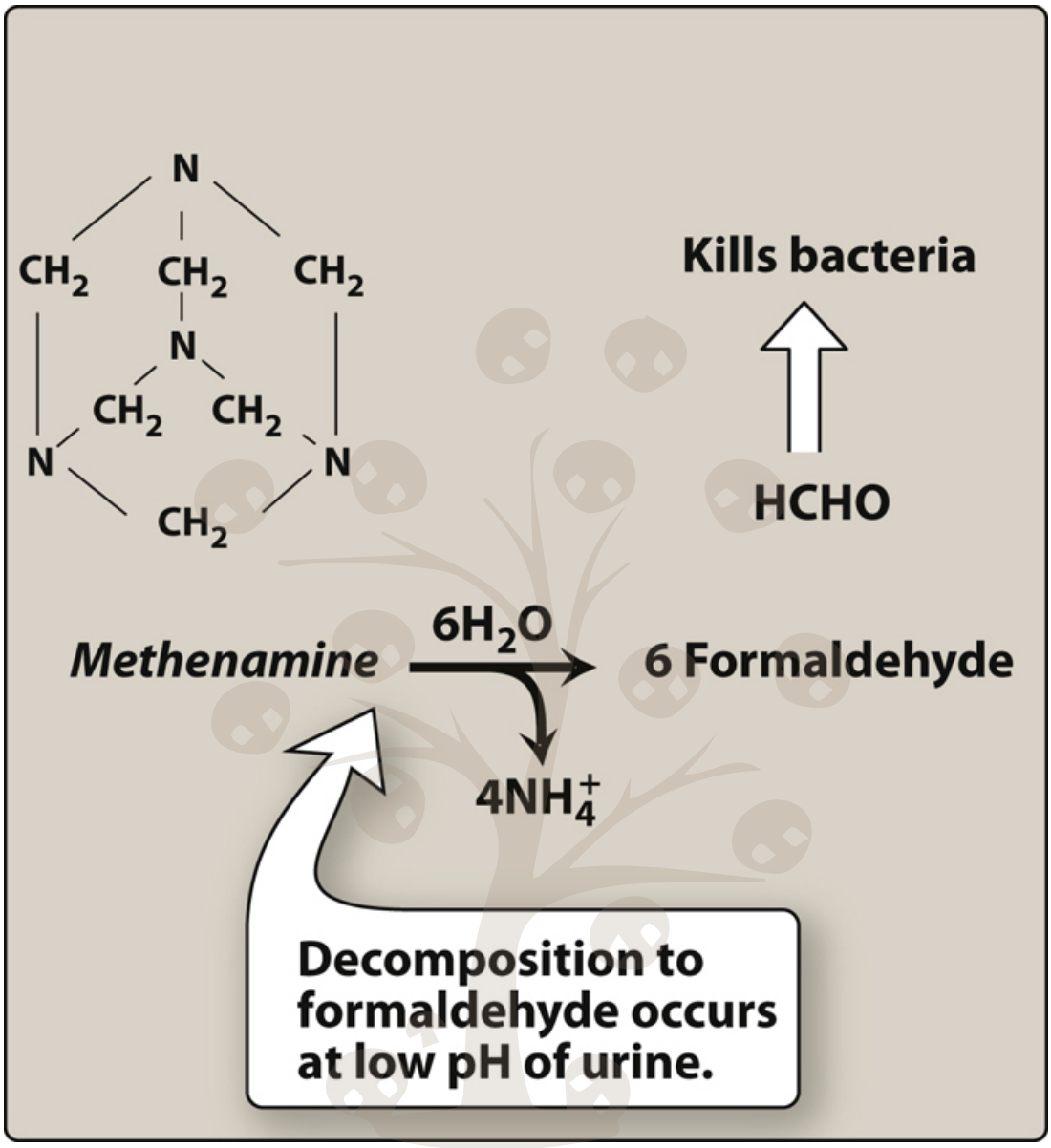

Figure 31.14 Formation of formaldehyde from *methenamine* at acid pH.

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2.Antibacterial spectrum: *Methenamine* is primarily used for chronic suppressive therapy to reduce the frequency of UTIs. *Methenamine* is active against E. coli, Enterococcus spp., and Staphylococcus spp. It has some activity against gram-negative fermenting and nonfermenting bacteria (Proteus spp. and P. aeruginosa, respectively); however, urine pH must be kept acidic to achieve bactericidal activity. Proteus

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spp. have the ability to raise the pH in urine through urease activity, thus inhibiting the conversion of *methenamine* to formaldehyde. The main benefit of *methenamine* is the lack of selection for resistant organisms.

3.Pharmacokinetics: *Methenamine* is orally absorbed, with up to 30% decomposing in gastric juices, unless protected by enteric coating. It reaches the urine through tubular secretion and glomerular filtration. Concentrations are sufficient to treat susceptible organisms. Due to ammonia formation, use should be avoided in hepatic insufficiency.

4.Adverse effects: The major adverse effect of *methenamine* is gastrointestinal distress, although at higher doses, albuminuria, hematuria, and rashes may develop. *Methenamine mandelate* is contraindicated in patients with renal insufficiency, because mandelic acid may precipitate. The *methenamine hippurate* formulation should be used instead. [Note: Sulfonamides, such as *TMP/SMX*, must not be used concomitantly with *methenamine.* The combination increases the risk of crystalluria and mutual antagonism.]

B. Nitrofurantoin

1.Mechanism of action: *Nitrofurantoin* [NYE-troe-fue-RAN-toin] was introduced into clinical practice for the management of cystitis in the early 1950s. *Nitrofurantoin* works by inhibiting DNA and RNA synthesis. For decades, it was rarely used, but was resurrected due to increasing antibiotic resistance among *Enterobacteriaceae* and is considered first-line therapy for uncomplicated cystitis.

2.Antimicrobial spectrum: *Nitrofurantoin* is bactericidal against most common gram-negative and gram-positive urinary tract pathogens. Susceptible organisms include *Enterobacteriaceae* (E. coli, Klebsiella spp.,), Enterococcus spp., and Staphylococcus spp.

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3.Pharmacokinetics: *Nitrofurantoin* is available in two oral formulations—*nitrofurantoin* macrocrystals and a combination of macrocrystals (25%) with *nitrofurantoin* monohydrate (75%). Following oral administration, *nitrofurantoin* is readily absorbed. The macrocrystal formulation is dosed four times daily. The macrocrystals have a slower rate of dissolution than *nitrofurantoin* monohydrate (also known as the microcrystalline formulation). To slow the release of *nitrofurantoin* from the combination product, the *nitrofurantoin* monohydrate is contained in a powder blend which forms a gel-like matrix through mixing with gastric juices. The matrix allows for a gradual release of *nitrofurantoin*, thereby reducing the dosing frequency to twice daily for the combination product. For each formulation, 40% of the drug is excreted unchanged in the urine.

4.Adverse effects: Common adverse events include nausea, vomiting, and diarrhea. Rare complications of therapy include pulmonary fibrosis, neuropathy, and autoimmune hepatitis. These events are observed with prolonged exposure greater than 1 month. Additionally, patients with impaired renal function should not receive *nitrofurantoin* due to an increased risk of adverse events.

Clinical Application 31.1 Treatment of Uncomplicated Cystitis

Historically, fluoroquinolones were considered first-line antibiotics for the treatment of uncomplicated cystitis. Due to the increasing emergence of resistance in gram-negative organisms including E. coli, the use of alternative urinary tract antiseptics/antimicrobials has increased. Of these, *nitrofurantoin* is an attractive therapeutic option due to its localized effects in the urinary tract; however, it is not suitable for more invasive UTIs such as pyelonephritis. A typical course of *nitrofurantoin* is 5 days. In addition to *nitrofurantoin*, other antimicrobials currently recommended as first-line options for uncomplicated cystitis include *TMP/SMX* (3-day course) and *fosfomycin* (single dose). *TMP/SMX* should be avoided in areas where resistant strains of E. coli are prevalent (>20%).

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C. Fosfomycin

Fosfomycin [fos-foe-MYE-sin] is a synthetic derivative of phosphonic acid. It blocks cell wall synthesis by inhibiting the enzyme enolpyruvyl transferase, a key step in peptidoglycan synthesis. *Fosfomycin* exhibits bactericidal activity, and it has been shown to reduce the adherence of bacteria to the urinary epithelium. This agent is considered first-line therapy for acute cystitis, and it is administered as a one-time oral dose. More information about this agent is available in Chapter 29.

Chapter Summary

- Fluoroquinolones are bactericidal through inhibition of DNA gyrase in gram-negative bacteria and topoisomerase IV in gram-positive organisms. These agents are utilized for many types of infections due to their broad spectrum of activity, wide distribution to tissues, and high oral bioavailability.
- Adverse reactions to fluoroquinolones include nausea, vomiting, and photosensitivity. These agents may prolong the QT_c interval, and they carry boxed warnings for tendinitis, tendon rupture, peripheral neuropathy, and CNS effects.
- Given the emergence of resistance and increasing reports of adverse events, fluoroquinolones should be reserved for more serious types of infections where alternatives are not suitable.
- Sulfonamide antimicrobials inhibit de novo synthesis of folate. Because of their structural similarity, sulfonamides compete with PABA to inhibit dihydropteroate synthetase and, ultimately, inhibit the genesis of bacterial dihydrofolic acid.
- Rash, photosensitivity, hypersensitivity reactions, crystalluria, and hemolytic anemia are adverse effects associated with the sulfonamides.
- *Trimethoprim* is an inhibitor of bacterial dihydrofolate reductase, thereby preventing the formation of the metabolically active form of folic acid (tetrahydrofolic acid) needed for normal bacterial cell function. This agent is most often used in combination with *sulfamethoxazole.*
- *TMP/SMX* remains a useful antimicrobial in the treatment of multiple types of infections, including UTIs, skin and soft tissue infections, and lower respiratory tract infections.
- *Nitrofurantoin* is a commonly used antibiotic for the treatment of uncomplicated cystitis; however, it should be avoided in patients with renal

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dysfunction or more invasive genitourinary tract infections.

STUDY QUESTIONS

Choose the ONE best answer.

31.1 A 32-year-old man presents to an outpatient clinic with a 5-day history of productive cough, purulent sputum, and shortness of breath. He is diagnosed with community-acquired pneumonia (CAP). It is noted that this patient has a severe ampicillin allergy (anaphylaxis). Which of the following is an acceptable treatment for this patient?

A. Levofloxacin
B. Ciprofloxacin
C. Penicillin VK
D. Nitrofurantoin

Correct answer = A. *Streptococcus pneumoniae* is a common cause of CAP, and the respiratory fluoroquinolones levofloxacin and moxifloxacin provide good coverage. Ciprofloxacin does not cover S. pneumoniae well and is a poor choice for the treatment of CAP. Penicillin would be a poor choice due to allergy. Nitrofurantoin has no clinical utility for respiratory tract infections.

31.2 Which of the following drugs is correctly matched with the appropriate adverse effect?

A. Levofloxacin—pulmonary fibrosis
B. Nitrofurantoin—hepatic encephalopathy
C. TMP/SMX—hyperkalemia
D. Methenamine—nystagmus

Correct answer = C. Hyperkalemia may be caused by TMP/SMX due to the trimethoprim potassium-sparing effect. Pulmonary fibrosis is an adverse effect associated with nitrofurantoin use. Hepatic encephalopathy may be related to

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therapy with methenamine in patients with hepatic insufficiency, not those that take nitrofurantoin. Nystagmus is not associated with methenamine therapy.

31.3 A 55-year-old man presents to primary care clinic with an erythematous and tender abscess on his left thigh. He has a history of MRSA skin infections. Which of the following is an appropriate antibiotic for empiric treatment?

A. Ciprofloxacin
B. TMP/SMX
C. Methenamine
D. Cephalexin

Correct answer = B. TMP/SMX is the only agent with reliable activity against MRSA. Methenamine is a urinary tract antiseptic and is not appropriate for the treatment of a skin and soft tissue infection. Ciprofloxacin does have some minor activity, but resistance has readily increased and it is no longer a valid recommendation. Cephalexin does not have activity against MRSA.

31.4 A 21-year-old marathon runner reports to the clinic with acute Achilles tendon rupture. The nurse noted that the patient recently took an antibiotic for community-acquired pneumonia. Which of the following antibiotics may have contributed to tendon rupture?

A. Amoxicillin/clavulanate
B. Cefdinir
C. Levofloxacin
D. Minocycline

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Correct answer = C. Fluoroquinolones (levofloxacin) are associated with tendon ruptures and tendinopathy. The other agents are not associated with this adverse effect.

31.5 A 56-year-old woman with acute cystitis presents to the clinic for assessment. She has a past medical history of hypertension, hypothyroidism, chronic kidney disease, and

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allergy to sulfa. Which of the following is the greatest concern for use of nitrofurantoin in this patient?

A. Age
B. Allergy to sulfa
C. Chronic kidney disease
D. Hypertension

Correct answer = C. The key issue with nitrofurantoin is that it should not be administered in patients with poor kidney function due to an increased risk of adverse effects. Nitrofurantoin is not a sulfa drug, so allergy to sulfa is not a concern. The patient is not of advanced age where increased adverse effects might be a concern, and hypertension is not a contraindication to use of this agent.

31.6 A 24-year-old woman with dysuria and urinary urgency is diagnosed with uncomplicated cystitis. The medical record reveals an anaphylactic allergy to cephalosporins and a history of medication noncompliance. Which of the following is the most appropriate for the treatment of her cystitis?

A. Moxifloxacin
B. Nitrofurantoin macrocrystals
C. Fosfomycin
D. Ceftriaxone

Correct answer = C. Single-dose fosfomycin is recommended in uncomplicated cystitis. In a patient with a history of noncompliance, it is ideal to use an agent that only requires one-time administration. Although nitrofurantoin is also a preferred agent, the macrocrystal formulation is not ideal due to four-times daily dosing. Moxifloxacin does not concentrate well into the urine, and ceftriaxone is not an ideal agent due to the documented cephalosporin allergy.

31.7 A 47-year-old patient is being treated for a hospital-acquired pneumonia caused by Pseudomonas aeruginosa. Which of the following is the most appropriate to include in the treatment regimen?

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A. Gemifloxacin
B. Levofloxacin
C. Moxifloxacin
D. TMP/SMX

Correct answer = B. While levofloxacin, moxifloxacin, and gemifloxacin are all considered effective for treating respiratory infections, only levofloxacin is effective at eradicating Pseudomonas aeruginosa. TMP/SMX lacks Pseudomonas spp. coverage and would be ineffective in treating hospital-acquired pneumonia due to *Pseudomonas aeruginosa*.

31.8 Which of the following best describes the mechanism of action of fluoroquinolones?

A. Denatures proteins and nucleic acids, resulting in bacterial cell death
B. Inhibits the incorporation of PABA into dihydrofolic acid precursors
C. Prevents reduction of dihydrofolate to tetrahydrofolate
D. Interferes with DNA replication by binding to DNA gyrase and topoisomerase IV

Correct answer = D. Methenamine salts are hydrolyzed to ammonia and formaldehyde in acidic urine (pH ≤ 5.5). Formaldehyde denatures proteins and nucleic acids, resulting in bacterial cell death. Sulfamethoxazole inhibits the incorporation of PABA into dihydrofolic acid precursors, and trimethoprim prevents reduction of dihydrofolate to tetrahydrofolate.

31.9 Which of the following is an adverse event associated with the use of sulfa antibiotics?

A. Crystalluria
B. QT_c prolongation
C. Peripheral neuropathy
D. Visual disturbances

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Correct answer = A. Of the choices, only crystalluria is associated with sulfa antibiotics. QT_c prolongation is associated with fluoroquinolones. Peripheral neuropathy is an uncommon complication with nitrofurantoin or fluoroquinolones, and visual disturbances are not associated with sulfa antibiotics.

31.1A 57-year-old patient reports to the clinic with signs and symptoms consistent with acute simple cystitis. The patient reports taking methenamine for chronic suppressive therapy to reduce the frequency of UTIs. Which of the following options is the best agent to manage her acute simple cystitis?

A. Nitrofurantoin
B. TMP/SMX
C. Levofloxacin
D. Delafloxacin

Correct answer = A. Of the available choices, nitrofurantoin is the best option. While typically nitrofurantoin and TMP/SMX are both first-line options for acute simple cystitis, a major drug interaction between TMP/SMX and methenamine would make TMP/SMX an incorrect choice. Levofloxacin should be reserved for more serious infections because of concerns for increased resistance. Delafloxacin is used to treat community-acquired pneumonia, not acute simple cystitis.

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32

Antimycobacterial Drugs

Charles A. Peloquin, Eric F. Egelund

I. OVERVIEW

Mycobacteria are rod-shaped aerobic bacilli that multiply slowly, every 18 to 24 hours in vitro. Their cell walls contain mycolic acids, which give the genus its name. Mycolic acids are long-chain, β-hydroxylated fatty acids. Mycobacteria produce highly lipophilic cell walls that stain poorly with Gram stain. Once stained, the bacilli are not decolorized easily by acidified organic solvents. Hence, the organisms are called "acid-fast bacilli." Mycobacterial infections classically result in the formation of slow-growing, granulomatous lesions that cause tissue destruction anywhere in the body.

Mycobacterium tuberculosis can cause latent tuberculosis infection (LTBI) and the disease known as tuberculosis (TB). [Note: In LTBI, the patient is infected with *M. tuberculosis* without signs or symptoms of active TB disease.] TB is the leading infectious cause of death worldwide, and a quarter of the world's population is infected with TB. Increasing in frequency are diseases caused by nontuberculous mycobacteria (NTM). These species include Mycobacterium avium-intracellulare, Mycobacterium chelonae, Mycobacterium abscessus, Mycobacterium kansasii, and Mycobacterium fortuitum. Finally, Mycobacterium leprae causes leprosy.

TB treatment generally includes four first-line drugs (Figure 32.1). Second-line drugs are typically less effective, more toxic, and less extensively studied. These agents are used for patients who cannot

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tolerate the first-line drugs or who are infected with resistant TB. No drugs are specifically developed for NTM infections. Macrolides, rifamycins, and aminoglycosides are frequently included, but NTM regimens vary widely by organism.

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DRUGS USED TO TREAT TUBERCULOSIS

Ethambutol MYAMBUTOL
Isoniazid GENERIC ONLY
Pyrazinamide GENERIC ONLY
Rifabutin MYCOBUTIN
Rifampin RIFADIN
Rifapentine PRIFTIN

DRUGS USED TO TREAT TUBERCULOSIS (2ND LINE)

Amikacin GENERIC ONLY
Aminosalicylic acid PASER
Bedaquiline SIRTURO
Cycloserine SEROMYCIN
Ethionamide TRECATOR
Fluoroquinolones
Linezolid ZYVOX
Macrolides
Pretomanid GENERIC ONLY

DRUGS USED TO TREAT LEPROSY

Clofazimine LAMPRENE
Dapsone GENERIC ONLY
Rifampin (*Rifampicin*) RIFADIN

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Figure 32.1 Summary of drugs used to treat mycobacterial infections.

II. CHEMOTHERAPY FOR TUBERCULOSIS

M. tuberculosis is slow growing and requires treatment for months to years. LTBI can be treated with 12 once-weekly higher doses of *isoniazid* and *rifapentine*, 4 months of daily *rifampin*, 3 months of daily *rifampin* and *isoniazid*, or, as an alternative, for 6 or 9 months with *isoniazid* monotherapy. In contrast, active TB disease must be treated with several drugs. Treatment for drug-susceptible TB lasts for at least 6 months, while treatment of multidrug-resistant TB (MDR-TB) typically lasts for about 2 years. New MDR-TB regimens are now shortening treatment time to 6 to 9 months.

A. Strategies for addressing drug resistance

Populations of *M. tuberculosis* contain small numbers of organisms that are naturally resistant to a particular drug. Under selective pressure from inadequate treatment, especially from monotherapy, these resistant organisms can emerge as the dominant population. Figure 32.2 shows that resistance develops rapidly in TB patients given only *streptomycin.* Multidrug therapy is employed to suppress these resistant organisms. The first-line drugs *isoniazid*, *rifampin*, *ethambutol*, and *pyrazinamide* are preferred because of their high efficacy and acceptable incidence of toxicity. *Rifabutin* or *rifapentine* may replace *rifampin* under certain circumstances. Active disease always requires treatment with multidrug regimens and preferably three or more drugs with proven in vitro activity against the isolate. Although clinical improvement can occur in the first several weeks of treatment, therapy is continued much longer to eradicate “persister” organisms and to prevent relapse.

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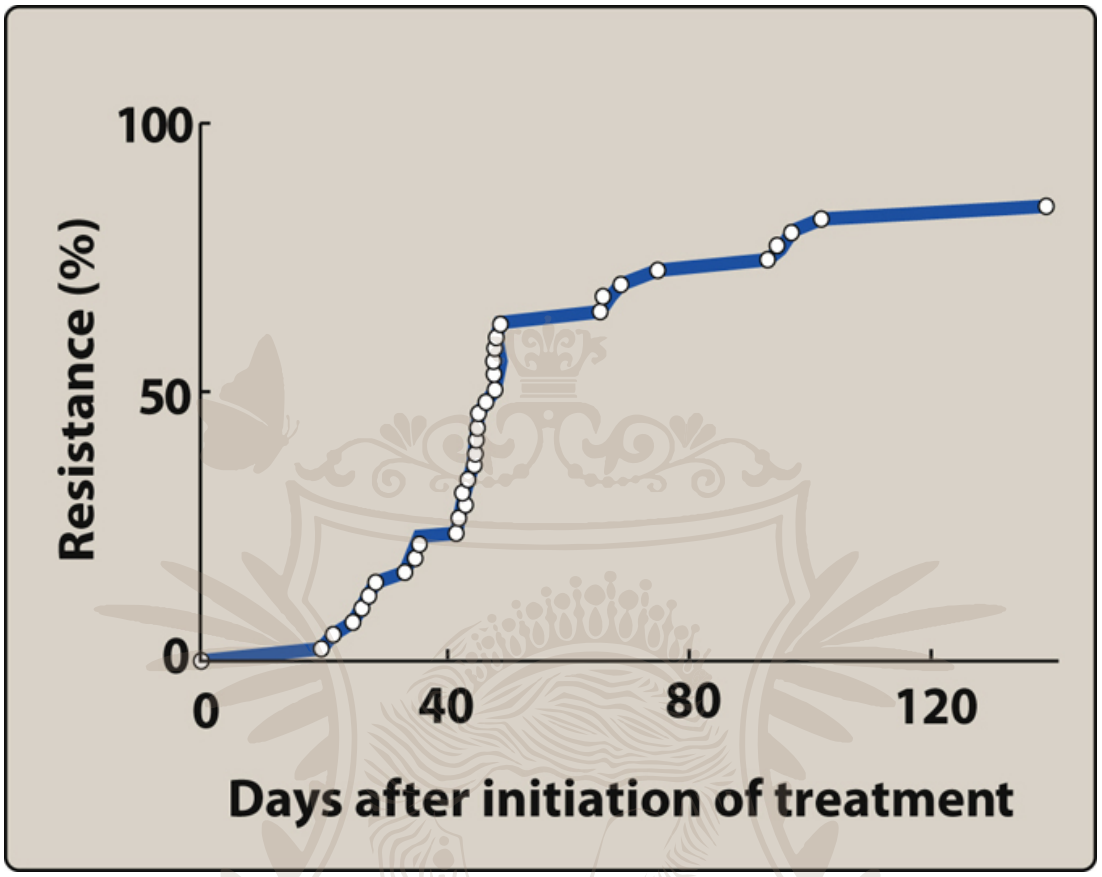

Figure 32.2 Cumulative percentage of strains of *Mycobacterium tuberculosis* showing resistance to *streptomycin*.

Standard short-course chemotherapy for active tuberculosis includes *isoniazid*, *rifampin*, *ethambutol*, and *pyrazinamide* for 2 months (the intensive phase), followed by *isoniazid* and *rifampin* for 4 months (the continuation phase; Figure 32.3). Once susceptibility data are available, the drug regimen can be individually tailored. Second-line regimens for MDR-TB (TB resistant to at least *isoniazid* and *rifampin*) include a fluoroquinolone (typically *levofloxacin* or *moxifloxacin*), any first-line drugs that remain active, and one or more of the following: *amikacin*, *cycloserine*, *ethionamide*, or *p-aminosalicylic acid.* For extensively drug-resistant TB (XDR-TB), other drugs such as *clofazimine* and *linezolid* may be employed empirically. A new

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regimen consisting of *bedaquiline, pretomanid*, and *linezolid* ("BPaL") may replace the use of the second-line drugs.

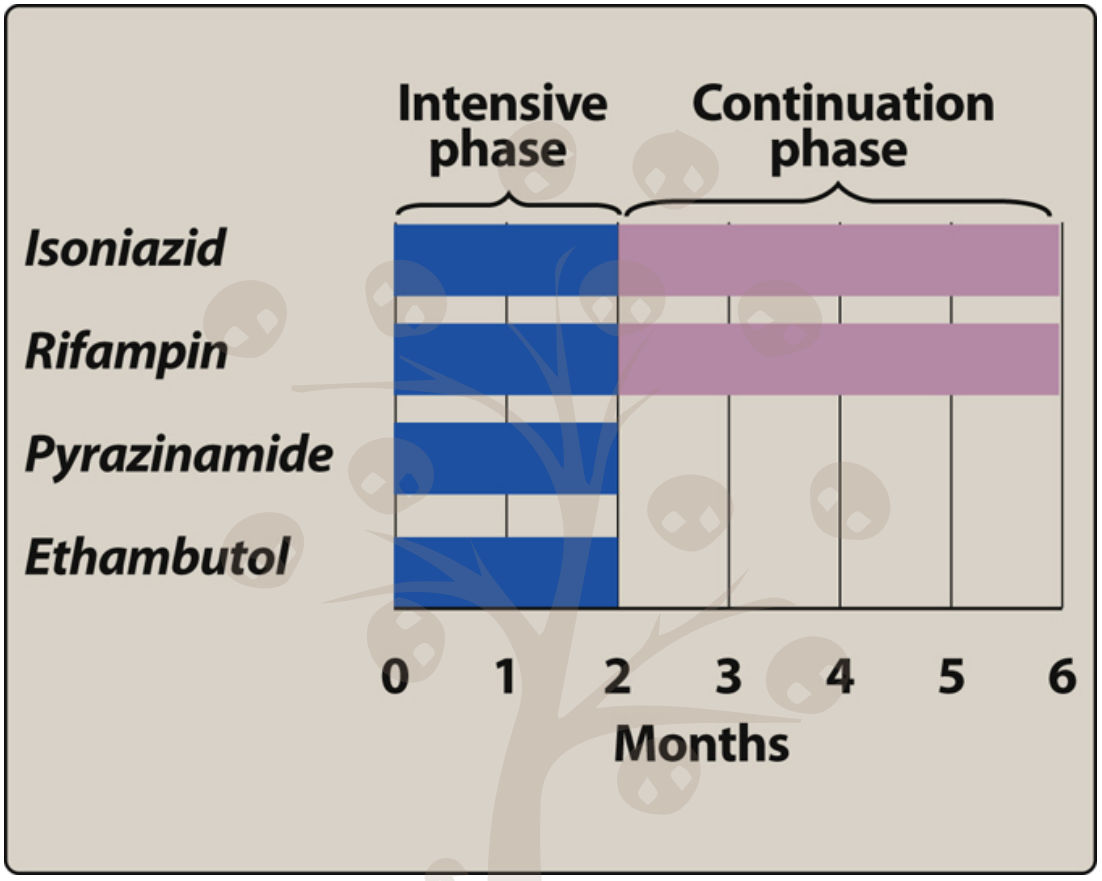

Figure 32.3 One of the several recommended multidrug schedules for the treatment of tuberculosis.

Patient adherence can be low when multidrug regimens last for 6 months or longer. One successful strategy for achieving better treatment completion rates is directly observed therapy (DOT). Patients take the medications under observation of a member of the healthcare team. DOT decreases drug resistance and improves cure rates. Most public health departments offer DOT services.

B. Isoniazid

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Isoniazid [eye-so-NYE-a-zid], along with *rifampin*, is one of the two most important TB drugs.

1.Mechanism of action: *Isoniazid* is a prodrug activated by a mycobacterial catalase–peroxidase (KatG). *Isoniazid* targets the enzymes acyl carrier protein reductase (InhA) and β-ketoacyl-ACP synthase (KasA), which are essential for the synthesis of mycolic acid. Inhibiting mycolic acid leads to a disruption in the bacterial cell wall.

2.Antibacterial spectrum: *Isoniazid* is specific for the treatment of M. tuberculosis, although M. kansasii may be susceptible at higher drug concentrations. Most NTM are resistant to *isoniazid.* The drug is particularly effective against rapidly growing bacilli and is also active against intracellular organisms.

3.Resistance: Resistance follows chromosomal mutations, including (1) mutation or deletion of KatG (producing mutants incapable of prodrug activation), (2) varying mutations of the acyl carrier proteins, or (3) overexpression of the target enzyme InhA. Cross-resistance may occur between *isoniazid* and *ethionamide*.

4.Pharmacokinetics: *Isoniazid* is readily absorbed after oral administration. Absorption is impaired if *isoniazid* is taken with food, particularly high-fat meals. The drug diffuses into all body fluids, cells, and caseous material (necrotic tissue resembling cheese that is produced in tuberculous lesions). Drug concentrations in the cerebrospinal fluid (CSF) are similar to those in the serum. *Isoniazid* undergoes *N*-acetylation and hydrolysis, resulting in inactive products. *Isoniazid* acetylation is genetically regulated, with fast acetylators exhibiting a 90-minute serum half-life, as compared with 3 to 4 hours for slow acetylators (Figure 32.4). Excretion is through glomerular filtration and secretion, predominantly as

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metabolites (Figure 32.5). Slow acetylators excrete more of the parent compound.

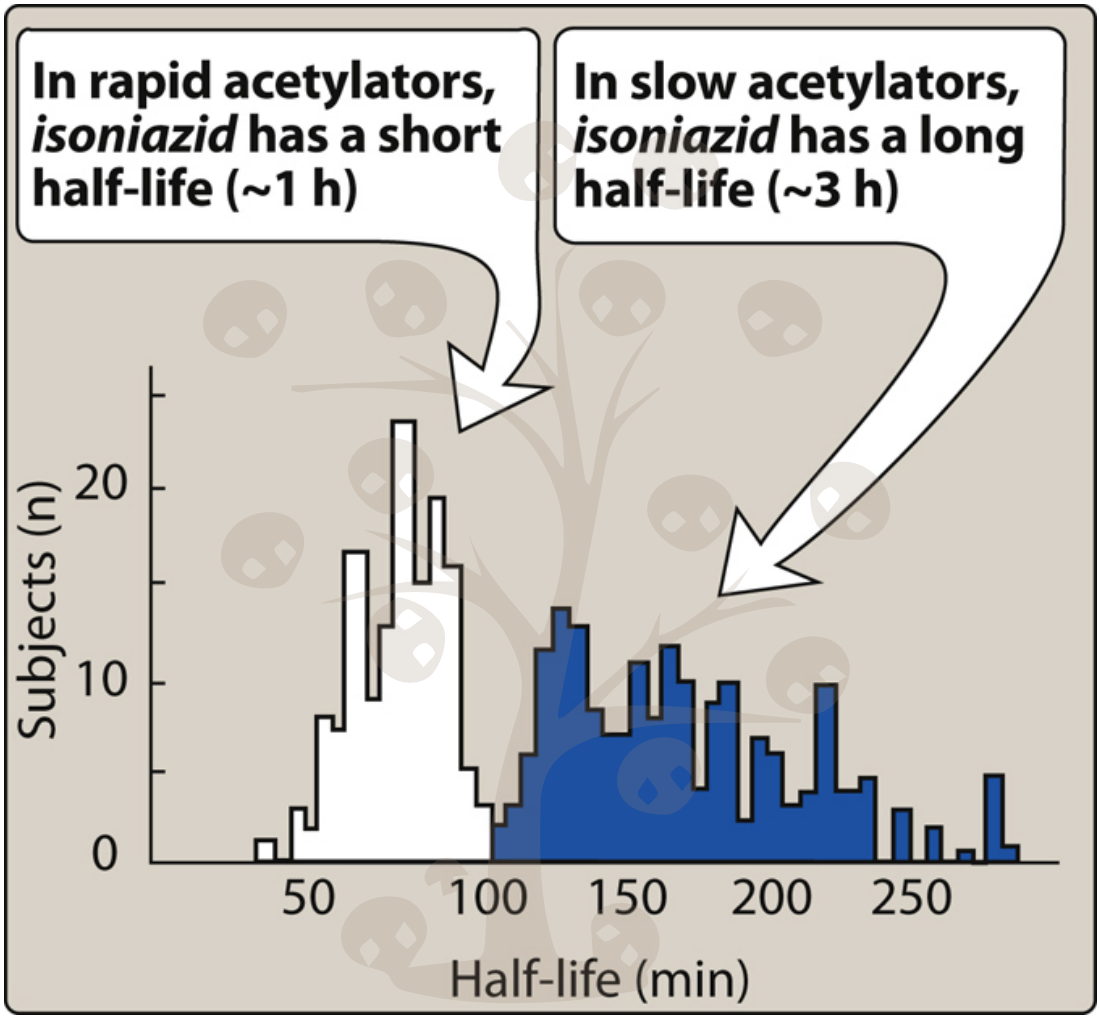

Figure 32.4 Bimodal distribution of *isoniazid* half-lives caused by rapid and slow acetylation of the drug.Data from D. A.Evans , K. A.Maley , and V. A.McRusick . Genetic control of isoniazid metabolism in man. *Br. Med. J*. 2: 485 (1960).

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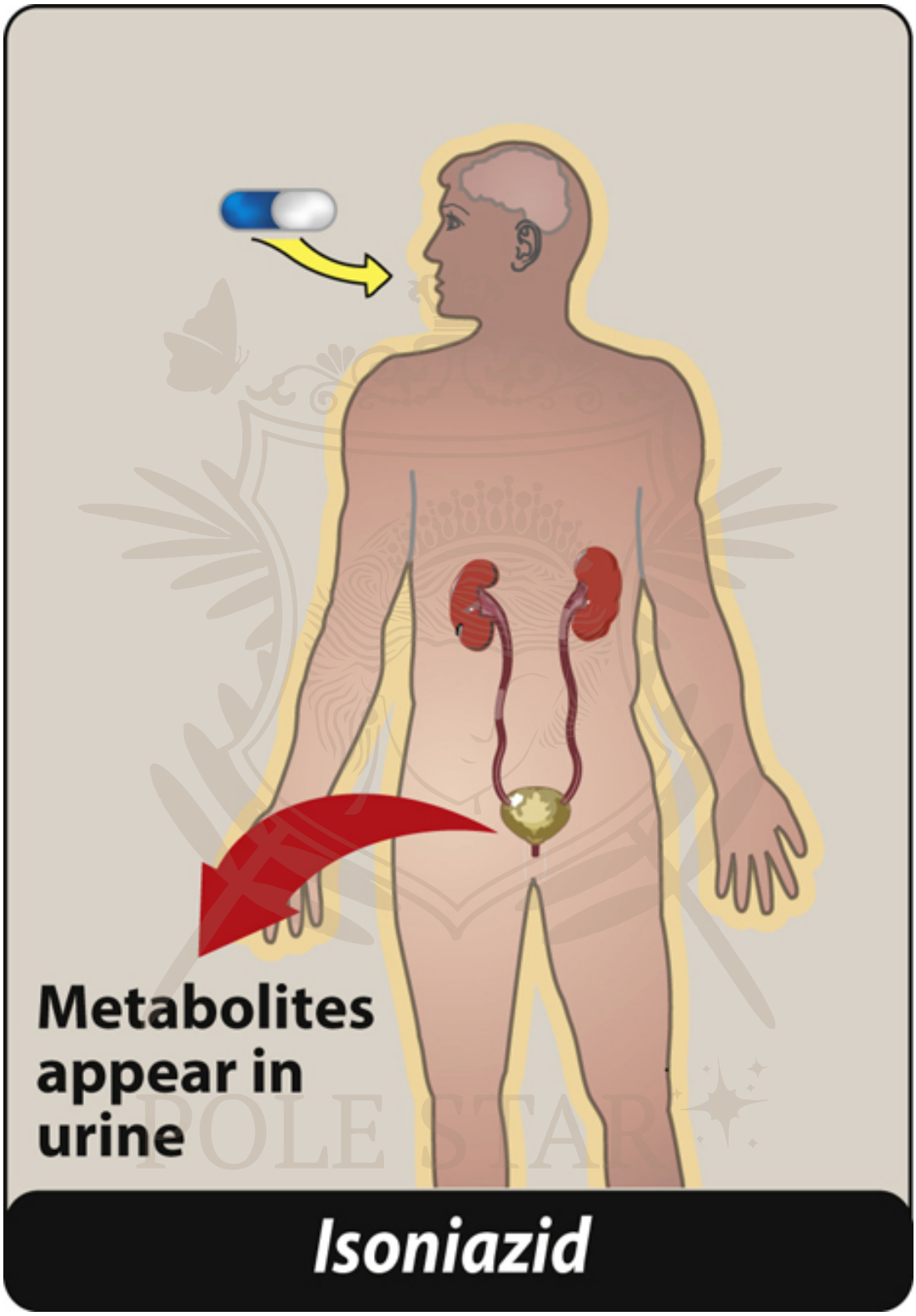

Figure 32.5 Administration and fate of *isoniazid*.

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5.Adverse effects: Hepatitis is the most serious adverse effect associated with *isoniazid.* If hepatitis goes unrecognized, and if *isoniazid* is continued, it can be fatal. The incidence increases with age (greater than 35 years old), among patients who also take *rifampin*, or among those who drink alcohol daily. Peripheral neuropathy, manifesting as paresthesia of the hands and feet, appears to be due to a relative pyridoxine deficiency caused by *isoniazid.* This can be avoided by daily supplementation of pyridoxine (vitamin B_6). Central nervous system (CNS) adverse effects can occur, including convulsions in patients prone to seizures. Hypersensitivity reactions with *isoniazid* include rashes and fever. Because *isoniazid* inhibits the metabolism of *carbamazepine* and *phenytoin* (Figure 32.6), *isoniazid* can potentiate the adverse effects of these drugs (for example, nystagmus and ataxia).

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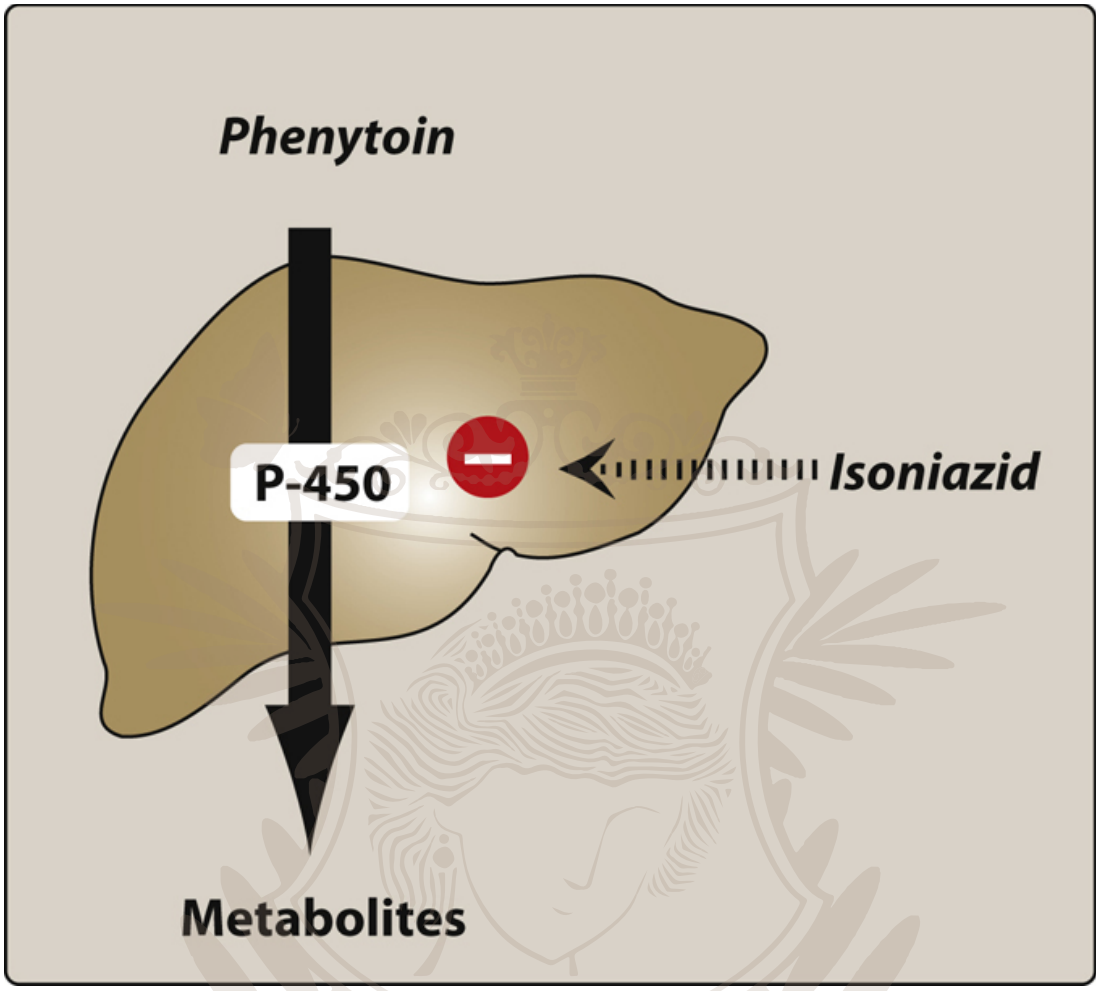

Figure 32.6 *Isoniazid* potentiates the adverse effects of *phenytoin*.

C. Rifamycins: rifampin, rifabutin, and rifapentine

Rifampin, *rifabutin*, and *rifapentine* are all considered rifamycins, a group of structurally similar macrocyclic antibiotics, which are first-line oral agents for tuberculosis.

1. **Rifampin:** *Rifampin* [ri-FAM-pin] has broader antimicrobial activity than *isoniazid* and can be used as part of treatment for several different bacterial infections. Because resistant strains rapidly emerge during monotherapy, it is never given as a single agent in the treatment of active tuberculosis.

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a. Mechanism of action: *Rifampin* blocks RNA transcription by interacting with the β subunit of mycobacterial DNA-dependent RNA polymerase.

b. Antimicrobial spectrum: *Rifampin* is bactericidal for both intracellular and extracellular mycobacteria, including M. tuberculosis, and NTM, such as M. kansasii and Mycobacterium avium complex (MAC). It is effective against many gram-positive and gram-negative organisms and is used prophylactically for individuals exposed to meningitis caused by meningococci or Haemophilus influenzae. *Rifampin* also is highly active against M. leprae.

c. Resistance: Resistance to *rifampin* is caused by a genetic mutation in the bacterial RNA polymerase, resulting in reduced affinity for the drug.

d. Pharmacokinetics: Absorption is adequate after oral administration. Distribution of *rifampin* occurs to all body fluids and organs. Concentrations attained in the CSF are variable, often 10% to 20% of blood concentrations. The drug is taken up by the liver and undergoes enterohepatic recycling. *Rifampin* can induce hepatic cytochrome P450 enzymes and transporters (see Chapter 1), leading to numerous drug interactions. Unrelated to its effects on cytochrome P450 enzymes, *rifampin* undergoes autoinduction, leading to a shortened elimination half-life over the first 1 to 2 weeks of dosing. Elimination of *rifampin* and its metabolites is primarily through the bile and into the feces; a small percentage is cleared in the urine (Figure 32.7). [Note: Urine, feces, and other secretions have an orange-red color, so patients should be forewarned. Tears may stain soft contact lenses orange-red.]

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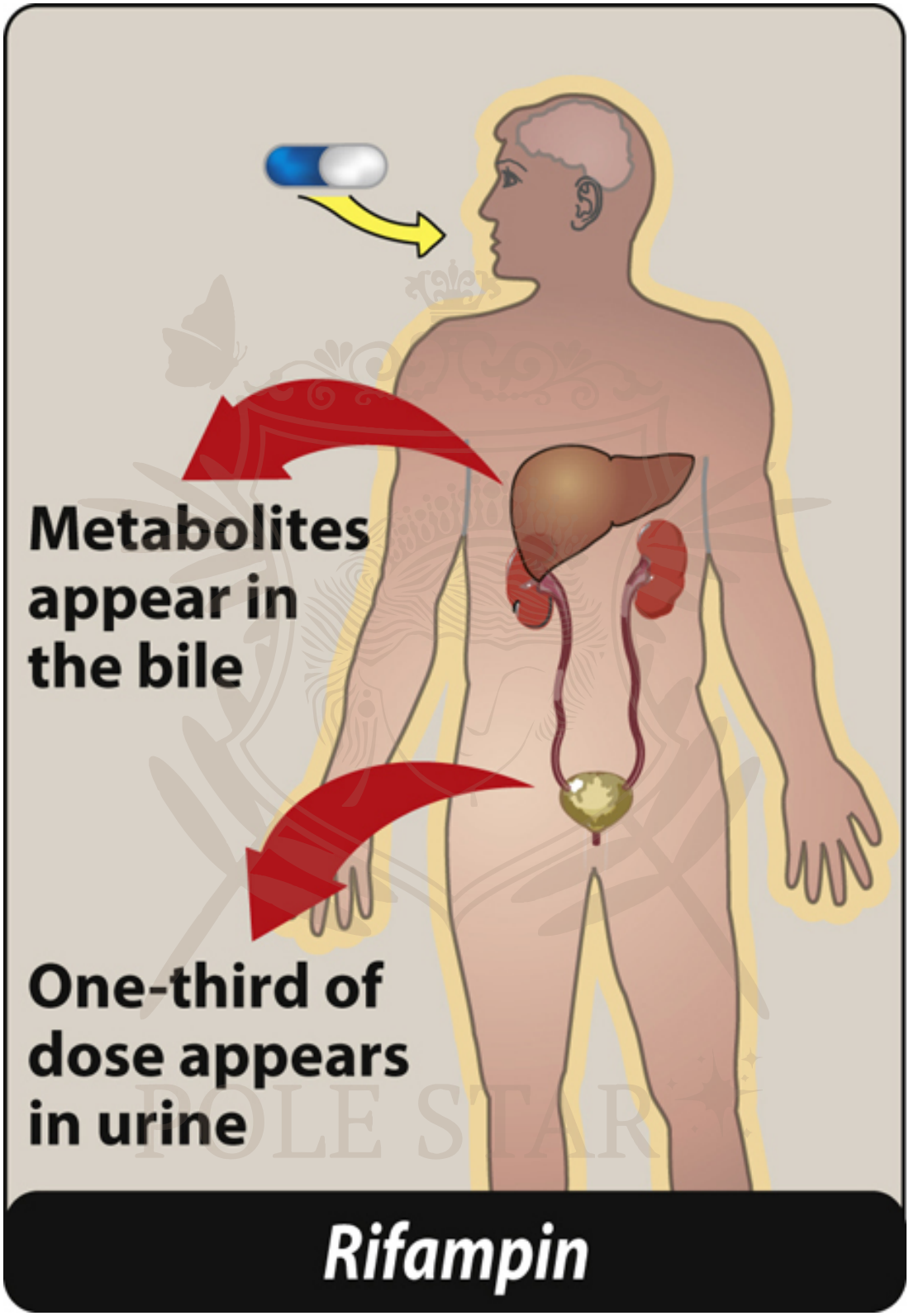
Metabolites appear in the bile
One-third of dose appears in urine
Rifampin

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Figure 32.7 Administration and fate of *rifampin*.[Note: Patient should be warned that urine and tears may turn orange-red in color.]

e. Adverse effects: *Rifampin* is generally well tolerated. The most common adverse reactions include nausea, vomiting, and rash. Hepatitis and death due to liver failure are rare. However, the drug should be used judiciously in older patients, alcoholics, or those with chronic liver disease. There is a modest increase in the incidence of hepatic dysfunction when *rifampin* is coadministered with *isoniazid* and *pyrazinamide.* When *rifampin* is dosed intermittently, especially with higher doses, a flu-like syndrome can occur, with fever, chills, and myalgia, sometimes extending to acute renal failure, hemolytic anemia, and shock.

f. Drug interactions: Because *rifampin* induces a number of phase I cytochrome P450 enzymes and phase II enzymes (see Chapter 1), it can decrease the half-lives of coadministered drugs that are metabolized by these enzymes (Figure 32.8). This may necessitate higher dosages for coadministered drugs, a switch to drugs less affected by *rifampin*, or replacement of *rifampin* with *rifabutin*.

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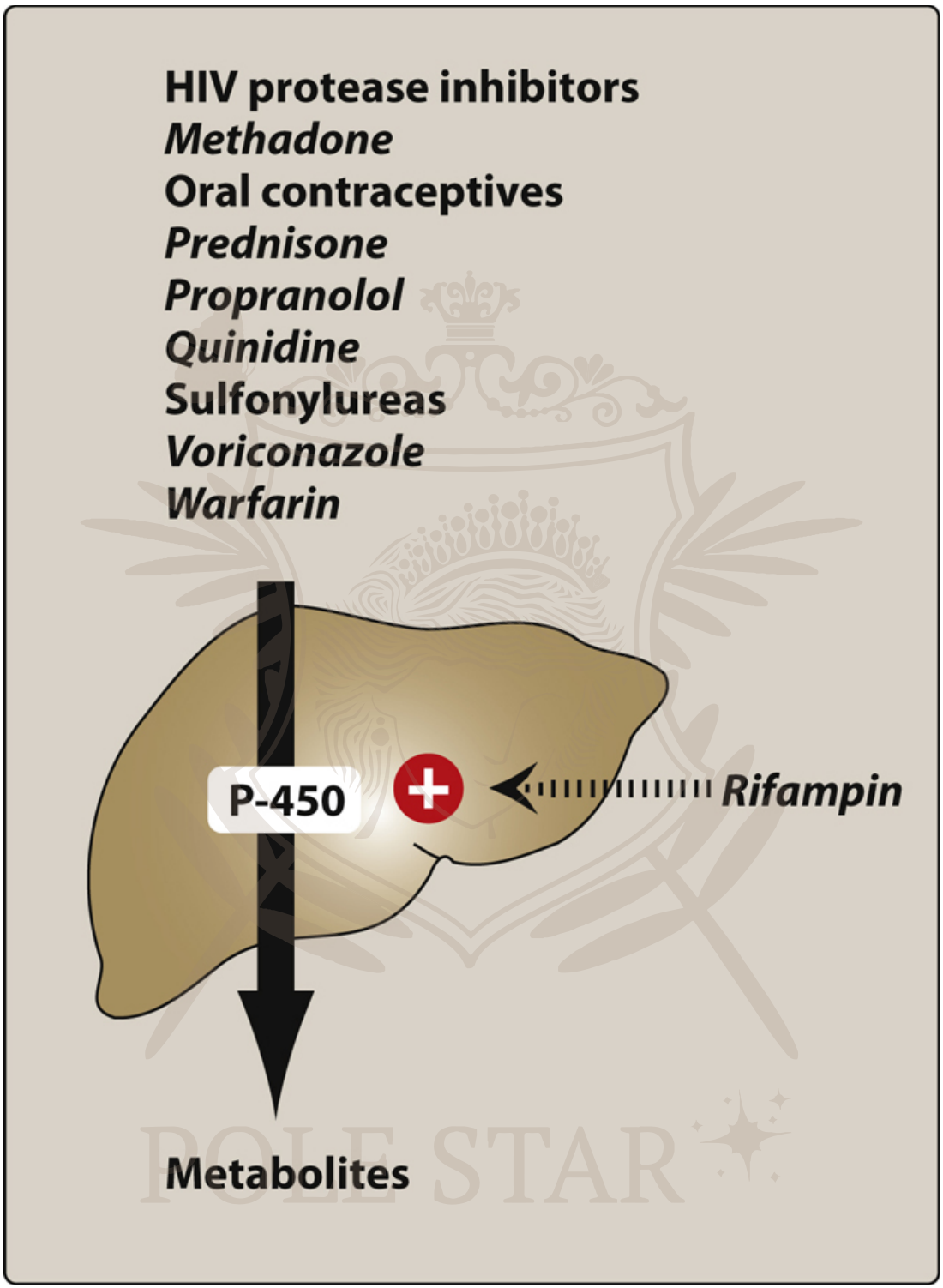

Figure 32.8 Induces cytochrome P450, which can decrease the half-lives of coadministered drugs that are metabolized by this system.

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2.Rifabutin: *Rifabutin* [rif-a-BYOO-tin], a derivative of *rifampin*, is preferred for TB patients coinfected with the human immunodeficiency virus (HIV) who are receiving protease inhibitors or several of the nonnucleoside reverse transcriptase inhibitors. *Rifabutin* is a less potent inducer (approximately 40% less) of cytochrome P450 enzymes, thus lessening drug interactions. *Rifabutin* has adverse effects similar to those of *rifampin* but can also cause uveitis, skin hyperpigmentation, and neutropenia.

3.Rifapentine: *Rifapentine* [rih-fa-PEN-teen] has a longer half-life than that of *rifampin.* In combination with *isoniazid*, *rifapentine* may be used once weekly in patients with LTBI and in select HIV-negative patients with minimal pulmonary TB.

D. Pyrazinamide

Pyrazinamide [peer-a-ZIN-a-mide] is a synthetic, orally effective short-course agent used in combination with *isoniazid*, *rifampin*, and *ethambutol.* The precise mechanism of action is unclear. *Pyrazinamide* must be enzymatically hydrolyzed by pyrazinamidase to pyrazinoic acid, which is the active form of the drug. Some resistant strains lack the pyrazinamidase enzyme. *Pyrazinamide* is active against tuberculosis bacilli in acidic lesions and in macrophages. The drug distributes throughout the body, penetrating the CSF. *Pyrazinamide* may contribute to liver toxicity. Uric acid retention is common, but rarely precipitates a gouty attack. Most of the clinical benefit from *pyrazinamide* occurs early in treatment. Therefore, this drug is usually discontinued after 2 months of a 6-month regimen.

E. Ethambutol

Ethambutol [e-THAM-byoo-tole] is bacteriostatic and specific for mycobacteria. *Ethambutol* inhibits arabinosyl transferase—an enzyme important for the synthesis of the mycobacterial cell wall. *Ethambutol* is used in combination with *pyrazinamide*, *isoniazid*, and *rifampin* pending culture and susceptibility data. [Note:

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Ethambutol may be discontinued if the isolate is determined to be susceptible to *isoniazid*, *rifampin*, and *pyrazinamide*.] *Ethambutol* distributes well throughout the body. Penetration into the CNS is variable, and it is questionably adequate for tuberculous meningitis. Both the parent drug and its hepatic metabolites are primarily excreted in the urine. The most important adverse effect is optic neuritis, which results in diminished visual acuity and loss of ability to discriminate between red and green. The risk of optic neuritis increases with higher doses and in patients with renal impairment. Visual acuity and color discrimination should be tested prior to initiating therapy and periodically thereafter. Uric acid excretion is decreased by *ethambutol*, and caution should be exercised in patients with gout.

Figure 32.9 summarizes some of the characteristics of first-line drugs.

DRUG	ADVERSE EFFECTS	COMMENTS
Ethambutol	Optic neuritis with blurred vision, red-green color blindness	Establish baseline visual acuity and color vision; test monthly.
Isoniazid	Hepatic enzyme elevation, hepatitis, peripheral neuropathy	Take baseline hepatic enzyme measurements; repeat if abnormal or patient is at risk or symptomatic. Clinically significant interaction with *phenytoin* and *carbamazepine*.
Pyrazinamide	Nausea, hepatitis, hyperuricemia, rash, joint ache, gout (rare)	Take baseline hepatic enzymes and uric acid measurements; repeat if abnormal or patient is at risk or symptomatic.
Rifampin	Hepatitis, GI upset, rash, flu-like syndrome, significant interaction with several drugs	Take baseline hepatic enzyme measurements and CBC; repeat if abnormal or patient is at risk or symptomatic. Warn patient that urine and tears may turn red-orange in color.

Figure 32.9 Some characteristics of first-line drugs used in treating tuberculosis.CBC = complete blood count; GI = gastrointestinal.

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F. Alternate second-line drugs

Para-aminosalicylic acid, *cycloserine*, *ethionamide*, *bedaquiline*, fluoroquinolones, macrolides, *linezolid*, and *pretomanid* are second-line TB drugs. Figure 32.10 summarizes some of the characteristics of second-line drugs.

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DRUG	ADVERSE EFFECTS	COMMENTS
Fluoroquinolones	GI intolerance, tendonitis, CNS toxicity including caffeine-like effects	Monitor LFTs, serum creatinine/BUN, QT interval prolongation. Avoid concomitant ingestion with antacids, multivitamins or drugs containing di- or trivalent cations.
Aminoglycosides, *Capreomycin*	Nephrotoxicity, ototoxicity	Not available orally. Monitor for vestibular, auditory and renal toxicity.
Macrolides	GI intolerance, tinnitus	Monitor LFTs, serum creatinine/BUN, QT interval prolongation. Monitor for drug interactions due to CYP inhibition (except *azithromycin*).
Ethionamide	GI intolerance, hepatotoxicity, hypothyroidism	Monitor LFTs, TSH. A majority of patients experience GI intolerance. Cross-resistance with *isoniazid* is possible.
Para-aminosalicylic acid (PAS)	GI intolerance, hepatotoxicity, hypothyroidism	Monitor LFTs, TSH. Patients with G6PD deficiency are at increased risk of hemolytic anemia.
Cycloserine	CNS toxicity	Close monitoring is needed for depression, anxiety, confusion, etc. Seizures may be exacerbated in patients with epilepsy. Monitor serum creatinine.

Figure 32.10 Some characteristics of second-line drugs used in treating tuberculosis.BUN = blood urea nitrogen; CNS = central nervous system; CYP = cytochrome; G6PD = glucose-6-phosphate dehydrogenase; GI = gastrointestinal; LFTs = liver function tests; TSH = thyroid-stimulating hormone.

1. Para-aminosalicylic acid: *Para-aminosalicylic* [a-mee-noe-sal-i-SIL-ik] *acid* works via folic acid inhibition. While largely replaced by *ethambutol* for drug-susceptible TB, *para-aminosalicylic acid* remains an important component of many regimens for MDR-TB.

2. Cycloserine: *Cycloserine* [SYE-kloe-SER-een] is an orally effective, tuberculostatic drug that disrupts d-alanine incorporation into the bacterial cell wall. It distributes well throughout body fluids, including the CSF. *Cycloserine* is primarily excreted unchanged in urine. Accumulation occurs with renal insufficiency. Adverse effects involve CNS disturbances (for example, lethargy, difficulty concentrating, anxiety, and suicidal tendency), and seizures may occur.

3. Ethionamide: *Ethionamide* [ETH-ee-ON-ah-MIDE] is a structural analog of *isoniazid* that also disrupts mycolic acid synthesis. The mechanism of action is not identical to

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isoniazid, but there is some overlap in the resistance patterns. *Ethionamide* is widely distributed throughout the body, including the CSF. Metabolism is extensive, most likely in the liver, to active and inactive metabolites. Adverse effects that limit its use include nausea, vomiting, and hepatotoxicity. Hypothyroidism, gynecomastia, alopecia, impotence, and CNS effects also have been reported.

4.Fluoroquinolones: The fluoroquinolones (see Chapter 31), specifically *moxifloxacin* and *levofloxacin*, have an important place in the treatment of MDR-TB. Some NTM also are susceptible.

5.Macrolides: The macrolides (see Chapter 30) *azithromycin* and *clarithromycin* are included in regimens for several NTM infections, including MAC. *Azithromycin* may be preferred for patients at greater risk for drug interactions, since *clarithromycin* is both a substrate and inhibitor of cytochrome P450 enzymes.

6.Bedaquiline: *Bedaquiline* [bed-AK-wi-leen], a diarylquinoline, is an ATP synthase inhibitor and may be used in conjunction with *linezolid* and *pretomanid* to treat MDR-TB or XDR-TB. *Bedaquiline* is administered orally, and it is active against many types of mycobacteria. *Bedaquiline* has a boxed warning for QT prolongation, and monitoring of the electrocardiogram is recommended. Elevations in liver enzymes have also been reported and liver function should be monitored during therapy. This agent is metabolized via CYP3A4, and administration with strong CYP3A4 inducers (for example, *rifampin*) should be avoided.

7.Linezolid: *Linezolid* [Li-NAY-zoh-lid], an oxazolidinone, inhibits bacterial protein synthesis (see Chapter 30). *Linezolid* is administered orally. Side effects include cytopenias and peripheral or ocular neuropathy. *Linezolid* is a monoamine oxidase inhibitor (MAOI) and use is contraindicated with

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agents that increase serotonin (for example, selective serotonin reuptake inhibitors and tricyclic antidepressants) due to the increased risk of serotonin syndrome.

8.Pretomanid: *Pretomanid* [pre-TOE-mah-nid], a nitroimidazooxazine, inhibits bacterial cell wall production. *Pretomanid* is administered orally. Adverse reactions seen in combination with *bedaquiline* and *linezolid* which should be monitored include nausea, hepatotoxicity, myelosuppression, and QT prolongation. This agent is partially metabolized via CYP3A4, and administration with strong CYP3A4 inducers (for example, *rifampin*) should be avoided.

III. DRUGS FOR LEPROSY

Leprosy (or Hansen disease) is uncommon in the United States; however, worldwide, it is a much larger problem (Figure 32.11). Leprosy can be treated effectively with *dapsone* and *rifampin* (Figure 32.12). *Clofazimine* may be added in some cases.

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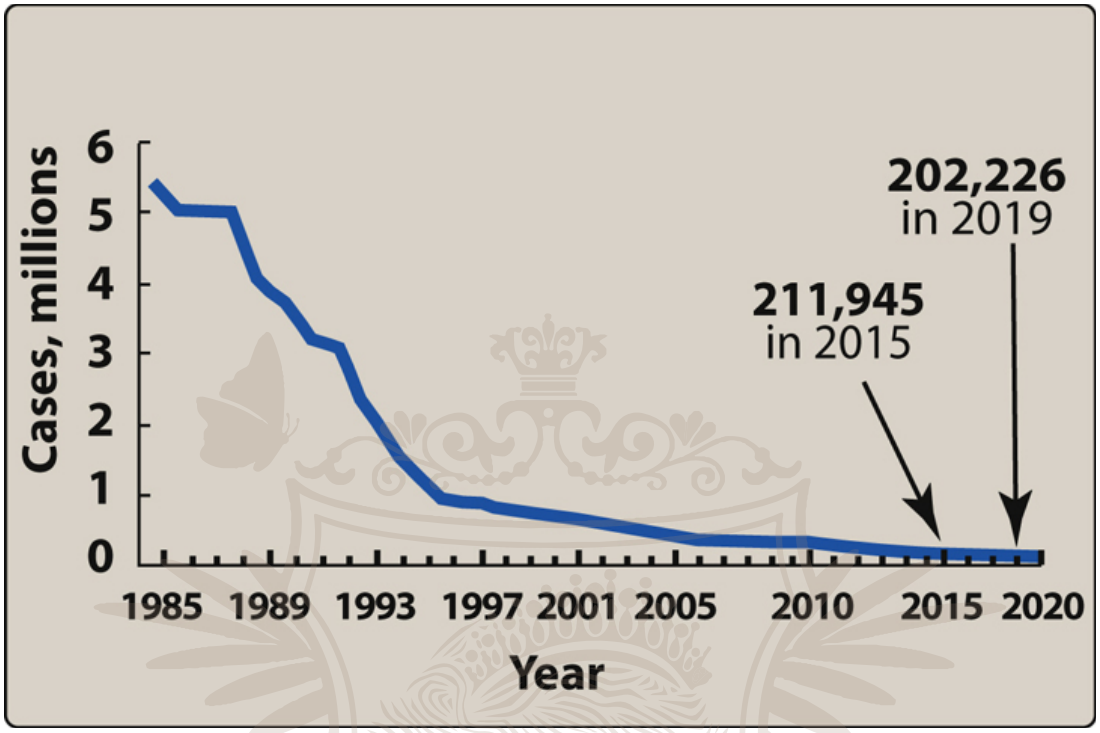

Figure 32.11 Reported prevalence of leprosy worldwide.

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Figure 32.12 Patient with leprosy before (**A**) and after treatment (**B**).

A. Dapsone

Dapsone [DAP-sone] is structurally related to the sulfonamides and similarly inhibits dihydropteroate synthase in the folate synthesis pathway. It is bacteriostatic for M. leprae, and resistant strains may be encountered. *Dapsone* also is used in the treatment of pneumonia caused by Pneumocystis jirovecii in immunosuppressed patients. The drug is well absorbed from the gastrointestinal tract and is distributed throughout the body, with high concentrations in the skin. The parent drug undergoes hepatic acetylation. Both parent drug and metabolites are eliminated in the urine. Adverse reactions include hemolysis (especially in patients with glucose-6-phosphate dehydrogenase deficiency), methemoglobinemia, and peripheral neuropathy.

B. Clofazimine

Clofazimine [kloe-FAZ-i-meen] is a phenazine dye. Its mechanism of action may involve binding to DNA, although alternative mechanisms have been proposed. Its redox properties may lead to the generation of cytotoxic oxygen radicals that are toxic to the bacteria. *Clofazimine* is bactericidal to M. leprae, and it has potentially useful activity against M. tuberculosis and NTM. The drug is recommended by the World Health Organization as part of a shorter regimen (9-12 months) for MDR-TB. Following oral absorption, *clofazimine* accumulates in tissues, allowing intermittent therapy but does not enter the CNS. Patients typically develop a pink to brownish-black discoloration of the skin and should be informed of this in advance. Eosinophilic and other forms of enteritis, sometimes requiring surgery, have been reported. *Clofazimine* has some anti-inflammatory and anti-immune activities. Thus, erythema nodosum leprosum may not develop in patients treated with this drug.

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Clinical Application 32.1: Tuberculosis Treatment

As opposed to the majority of infectious diseases, which require a short course of therapy with a single antibiotic, treatment of TB consists of a multidrug regimen for several months. Resistant tuberculosis (MDR-TB and XDR-TB) is even more difficult to treat, especially in resource-limited settings. Prevention of resistance, therefore, is key to reducing morbidity and mortality. Testing and treatment of LTBI via DOT, ensuring adherence to active TB treatment, and optimizing drug treatment (for example, via therapeutic drug monitoring) are key to reducing drug resistance. [Note: With DOT, the patient meets with the healthcare worker (in person or virtually) each time a dose of TB medication is needed and takes the TB medication while the healthcare worker watches. This helps to ensure adherence.]

Clinical Application 32.2: Nontuberculous Mycobacteria or Tuberculosis?

In the United States, the prevalence of NTM disease is greater than TB. NTM is acquired from the environment as opposed to TB, which is acquired through person-to-person contact. Respiratory specimens from patients who test positive for acid-fast bacilli may have a NTM infection rather than TB. Symptoms may also be similar. Drug treatment differs between NTM species and TB; therefore, appropriate identification of the species and an accurate diagnosis are important for distinguishing the disease states.

Chapter Summary

- Regimens for treatment of LTBI include: (1) 3 months of once-weekly *isoniazid* and *rifapentine*, (2) 4 months of daily *rifampin*, or (3) 3 months of daily *rifampin* and *isoniazid.*
- Active tuberculosis requires treatment with a minimum of four drugs for 6 months.
- A regimen consisting of *bedaquiline, pretomanid*, and *linezolid* (“BPaL”) is used to treat MDR-TB.

STUDY QUESTIONS

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Choose the ONE best answer.

32.1A 32-year-old woman was admitted to the hospital with a 4-week history of cough and fever. A chest radiograph showed left upper lobe cavitary infiltrate. Cultures of sputum yielded M. tuberculosis susceptible to all antimycobacterial drugs. The patient received self-administered isoniazid, rifampin, pyrazinamide, and ethambutol. Two weeks following initiation of therapy, the patient is concerned that her vision is blurry. Which of the following drugs is the most likely cause?

A. Isoniazid
B. Rifampin
C. Pyrazinamide
D. Ethambutol

Correct answer = D. Ethambutol, even at "standard" doses, can cause ocular toxicity, including blurred vision and red-green color blindness. Visual disturbances are reversible (weeks to months) if ethambutol is discontinued promptly.

32.2A 29-year-old cachectic woman taking isoniazid, pyrazinamide, ethambutol, and rifampin for tuberculosis presents to the emergency room (ER) complaining of paresthesias of her hands and feet. The ER physician diagnoses the paresthesias as an adverse effect to one of the patient's medications. What of the following is the cause and medication associated with paresthesias?

A. Riboflavin deficiency; Ethambutol
B. Thiamine deficiency; Rifampin
C. Pyridoxine deficiency; Isoniazid
D. Iron deficiency; Pyrazinamide

Correct answer = C. Peripheral neuropathy, manifesting as paresthesias of the hands and feet, results from a pyridoxine deficiency caused by the competitive inhibition of pyridoxine by isoniazid. This adverse effect of isoniazid is most

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commonly seen in malnourished, alcoholic, and diabetic patients. These patient populations should receive supplementation of 25 to 50 mg per day of pyridoxine (Vitamin B6) with concomitant administration of isoniazid. Riboflavin deficiency is not an adverse effect of ethambutol. Thiamine deficiency is not an adverse effect of rifampin. Iron deficiency is not an adverse effect of pyrazinamide.

32.3 A 23-year-old man was started on standard four-drug antimycobacterial therapy for treatment of active TB. He has epilepsy, which is controlled with carbamazepine. He has had no seizures in 5 years; however, upon return to clinic at 1 month, he reports having two seizures since his last visit. Which of the following drugs is most likely associated with the increased incidence of seizures?

A. Isoniazid
B. Rifampin
C. Pyrazinamide
D. Ethambutol

Correct answer = B. Rifampin is a potent inducer of cytochrome P450–dependent drug-metabolizing enzymes and may reduce the concentration of carbamazepine. None of the other drugs listed induce cytochrome P450 enzymes that could lower levels of carbamazepine.

32.4 A 26-year-old woman with HIV was recently diagnosed with active tuberculosis. Currently, she is on a stable HIV regimen consisting of atazanavir plus emtricitabine/tenofovir (a protease inhibitor and two nucleoside reverse transcriptase inhibitors). Which of the following is the most appropriate regimen for treatment of her tuberculosis?

A. Rifampin + isoniazid + pyrazinamide + ethambutol
B. Rifabutin + isoniazid + pyrazinamide + ethambutol
C. Rifapentine + isoniazid + pyrazinamide + ethambutol
D. Rifampin + moxifloxacin + pyrazinamide + ethambutol

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Correct answer = B. Rifabutin is recommended in place of rifampin in patients coinfected with HIV, since it is a less potent inducer of CYP enzymes than rifampin. However, rifabutin is a CYP3A4 substrate and "bidirectional" interactions may result. That is, other medications, such as the protease inhibitors, may affect the concentration of rifabutin, requiring dose adjustment of rifabutin or use of alternative HIV agents.

32.5 A 28-year-old man with MDR-TB is receiving the following medications for treatment: bedaquiline, linezolid, and pretomanid. Which of the following drug(s) in his regimen requires monitoring for QT prolongation?

A. Bedaquiline only
B. Linezolid only
C. Pretomanid only
D. Bedaquiline and pretomanid

Correct answer = D. Both bedaquiline and pretomanid have been associated with QT prolongation. The combination of both drugs may cause additive toxicity and should be closely monitored.

32.6 A 24-year-old man is diagnosed with latent TB. He is taking no medications at the moment. Which of the following regimens is most appropriate for treatment?

A. Isoniazid once daily for 9 months
B. Isoniazid once weekly for 9 months
C. Isoniazid and rifampin once weekly for 3 months
D. Isoniazid and rifapentine once weekly for 3 months

Correct answer = D. Regimens for treatment of latent tuberculosis infection (LTBI) include (1) 3 months of once-weekly isoniazid and rifapentine, (2) 4 months of daily rifampin, or (3) 3 months of daily rifampin and isoniazid.

32.7 Which of the following is correct regarding dapsone in the treatment of leprosy?

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A. Dapsone should not be used in patients with a deficiency in glucose-6-phosphate dehydrogenase (G6PD).
B. Peripheral neuropathy is one of the most common adverse effects seen with the drug.
C. Dapsone may cause skin discoloration over time.
D. Urine, saliva, tears, and sweat may be colored orange due to dapsone.

Correct answer = A. Dapsone should be used with caution in patients with G6PD deficiency due to the risk of hemolysis. Peripheral neuropathy is common with isoniazid. Clofazimine may cause skin discoloration during treatment for leprosy. Rifampin is a cause of discolored urine, saliva, and tears.

32.8 A 25-year-old woman being treated for XDR-TB is taking the following medications: clofazimine, pretomanid, linezolid, and bedaquiline. Other medications include fluoxetine for depression and montelukast for asthma. Which of the following medications may potentially interact with fluoxetine?

A. Ethionamide
B. Pretomanid
C. Linezolid
D. Bedaquiline

Correct answer = C. Linezolid is a weak MAO inhibitor and should be used cautiously with selective serotonin reuptake inhibitors such as fluoxetine due to the increased risk of serotonin syndrome.

32.9 A 46-year-old man with active tuberculosis is to be initiated on the four-drug regimen of isoniazid, rifampin, pyrazinamide, and ethambutol. The patient reports no other conditions except gout. Which of the following pair of antituberculosis drugs has the potential to worsen his gout?

A. Rifampin and isoniazid
B. Ethambutol and pyrazinamide
C. Rifampin and ethambutol

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D. Isoniazid and ethambutol

Correct answer = B. Ethambutol and especially pyrazinamide both may increase uric acid concentrations and have the potential to precipitate gouty attacks. Pyrazinamide- and ethambutol-induced hyperuricemia may be controlled by use of antigout medications, such as xanthine oxidase inhibitors. Symptoms of gout must be monitored closely.

32.10 A 36-year-old man with multidrug-resistant tuberculosis is being treated with the following agents: moxifloxacin, cycloserine, pyrazinamide, ethionamide, and *p*-aminosalicylic acid. His physician recently noticed that he has developed an enlargement of the left breast, which is quite painful. Which of the following medications is likely responsible?

A. Moxifloxacin
B. Cycloserine
C. Pyrazinamide
D. Ethionamide

Correct answer = D. Though rare, ethionamide has the potential to induce gynecomastia. Ethionamide should be replaced with a different medication and the pain treated if necessary.

POLE STAR

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33

Antifungal Drugs

Lindsey M. Childs-Kean, Vidhu Kariyawasam

I. OVERVIEW

Infectious diseases caused by fungi are called mycoses, and they are often chronic in nature. Mycotic infections may involve only the skin (cutaneous mycoses extending into the epidermis) or may cause subcutaneous or systemic infections. Unlike bacteria, fungi are eukaryotic, with rigid cell walls composed largely of chitin rather than peptidoglycan (a characteristic component of most bacterial cell walls). In addition, the fungal cell membrane contains ergosterol rather than the cholesterol found in mammalian membranes. These structural characteristics are useful targets for chemotherapeutic agents against mycoses. Fungi are generally resistant to antibiotics; conversely, bacteria are resistant to antifungal agents. The incidence of mycoses such as candidemia has been on the rise for the last few decades. This is attributed to an increased number of patients with chronic immune suppression due to organ transplantation, cancer chemotherapy, or human immunodeficiency virus (HIV) infection. Simultaneously, new therapeutic options have become available for the treatment of mycoses. Figure 33.1 summarizes clinically useful agents for cutaneous and systemic mycoses. Figure 33.2 lists the common pathogenic organisms of the Kingdom Fungi, and Figure 33.3 provides an overview of the mechanism of action of the various antifungal agents.

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DRUGS FOR SUBCUTANEOUS AND SYSTEMIC MYCOSES

Amphotericin B VARIOUS
Anidulafungin ERAXIS
Caspofungin CANCIDAS
Fluconazole DIFLUCAN
Flucytosine ANCOBON
Isavuconazole CRESEMBA
Itraconazole SPORANOX
Ketoconazole GENERIC ONLY
Micafungin MYCAMINE
Posaconazole NOXAFIL
Voriconazole VFEND

DRUGS FOR CUTANEOUS MYCOSES

Butenafine LOTRIMIN ULTRA, MENTAX
Butoconazole GYNAZOLE
Ciclopirox LOPROX, PENLAC
Clotrimazole LOTRIMIN AF, VARIOUS
Econazole ECOZA, SPECTAZOLE
Efinaconazole JUBLIA
Griseofulvin GRIS-PEG
Ketoconazole VARIOUS
Miconazole VARIOUS
Naftifine NAFTIN
Nystatin GENERIC ONLY
Oxiconazole OXISTAT
Sertaconazole ERTACZO
Sulconazole EXELDERM
Tavaborole KERYDIN
Terbinafine LAMISIL AT
Terconazole GENERIC ONLY
Tioconazole VAGISTAT-1
Tolnaftate TINACTIN

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Figure 33.1 Summary of antifungal drugs.

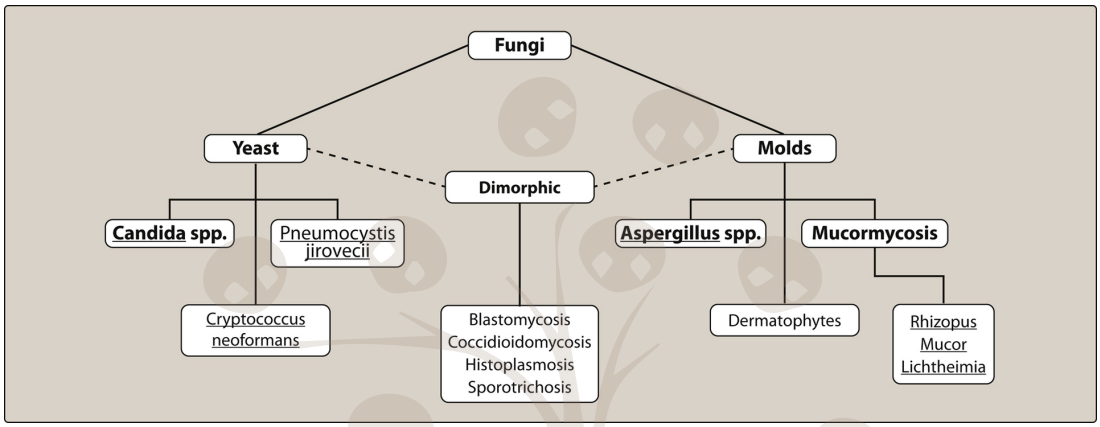

Figure 33.2 Common pathogenic organisms of Kingdom Fungi.

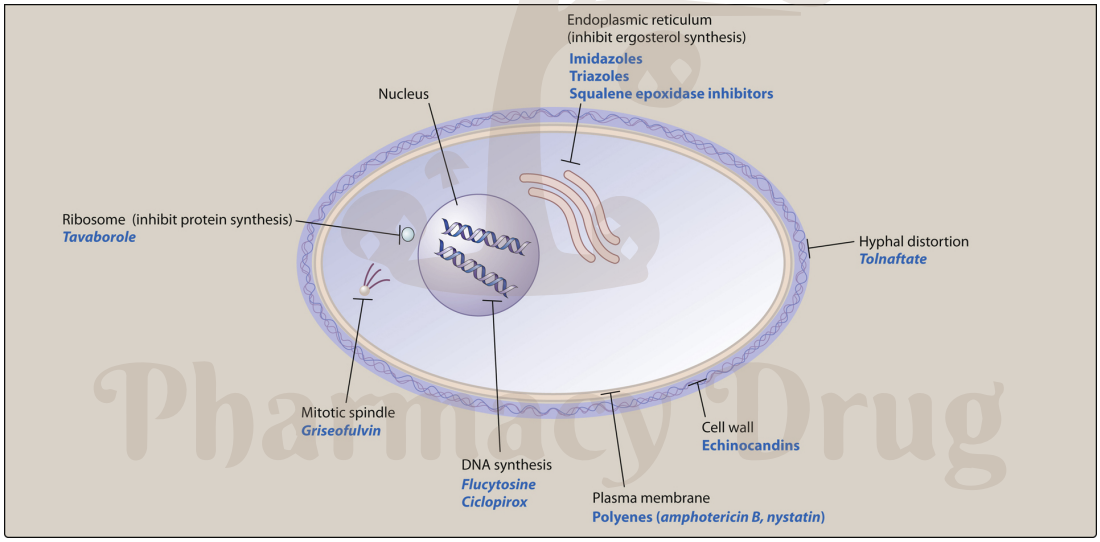

Figure 33.3 Cellular targets of antifungal drugs.

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II. DRUGS FOR SUBCUTANEOUS AND SYSTEMIC MYCOTIC INFECTIONS

A. Amphotericin B

Amphotericin [am-foe-TER-i-sin] *B* is a naturally occurring polyene antifungal produced by Streptomyces nodosus. In spite of its toxic potential, *amphotericin B* remains the drug of choice for the treatment of several life-threatening mycoses.

1. Mechanism of action: *Amphotericin B* binds to ergosterol in the plasma membranes of fungal cells. There, it forms pores (channels) that require hydrophobic interactions between the lipophilic segment of the polyene antifungal and the sterol (Figure 33.4). The pores disrupt membrane function, allowing electrolytes (particularly potassium) and small molecules to leak from the cell, resulting in cell death.

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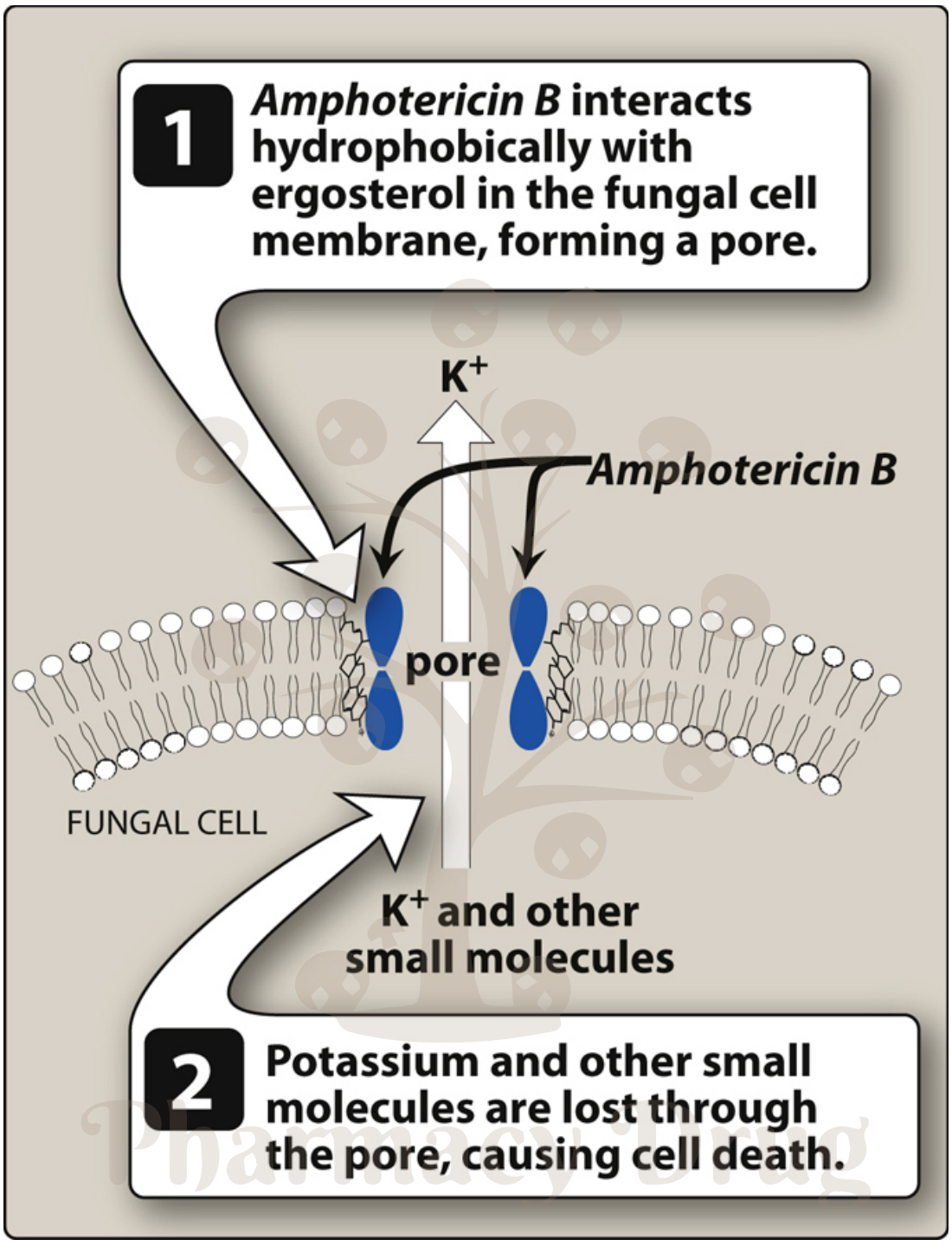

Figure 33.4 Model of a pore formed by *amphotericin B* in the lipid bilayer membrane.

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2.Antifungal spectrum: *Amphotericin B* is either fungicidal or fungistatic, depending on the organism and the concentration of the drug. It is effective against a wide range of fungi, including Candida albicans, Histoplasma capsulatum, Cryptococcus neoformans, Coccidioides immitis, Blastomyces dermatitidis, and many strains of Aspergillus. [Note: *Amphotericin B* is also used in the treatment of the protozoal infection leishmaniasis.]

3.Resistance: Fungal resistance to *amphotericin B*, although infrequent, is associated with decreased ergosterol content of the fungal membrane.

4.Pharmacokinetics: *Amphotericin B* is administered by slow intravenous (IV) infusion (Figure 33.5). *Amphotericin B* is insoluble in water and must be coformulated with sodium deoxycholate (conventional) or artificial lipids to form liposomes. The liposomal preparations are associated with reduced renal and infusion toxicity but are more costly. *Amphotericin B* is extensively bound to plasma proteins and is distributed throughout the body. Inflammation favors penetration into various body fluids, but little of the drug is found in the cerebrospinal fluid (CSF), vitreous humor, peritoneal fluid, or synovial fluid. Low levels of the drug and its metabolites are excreted primarily in the urine over a long period of time.

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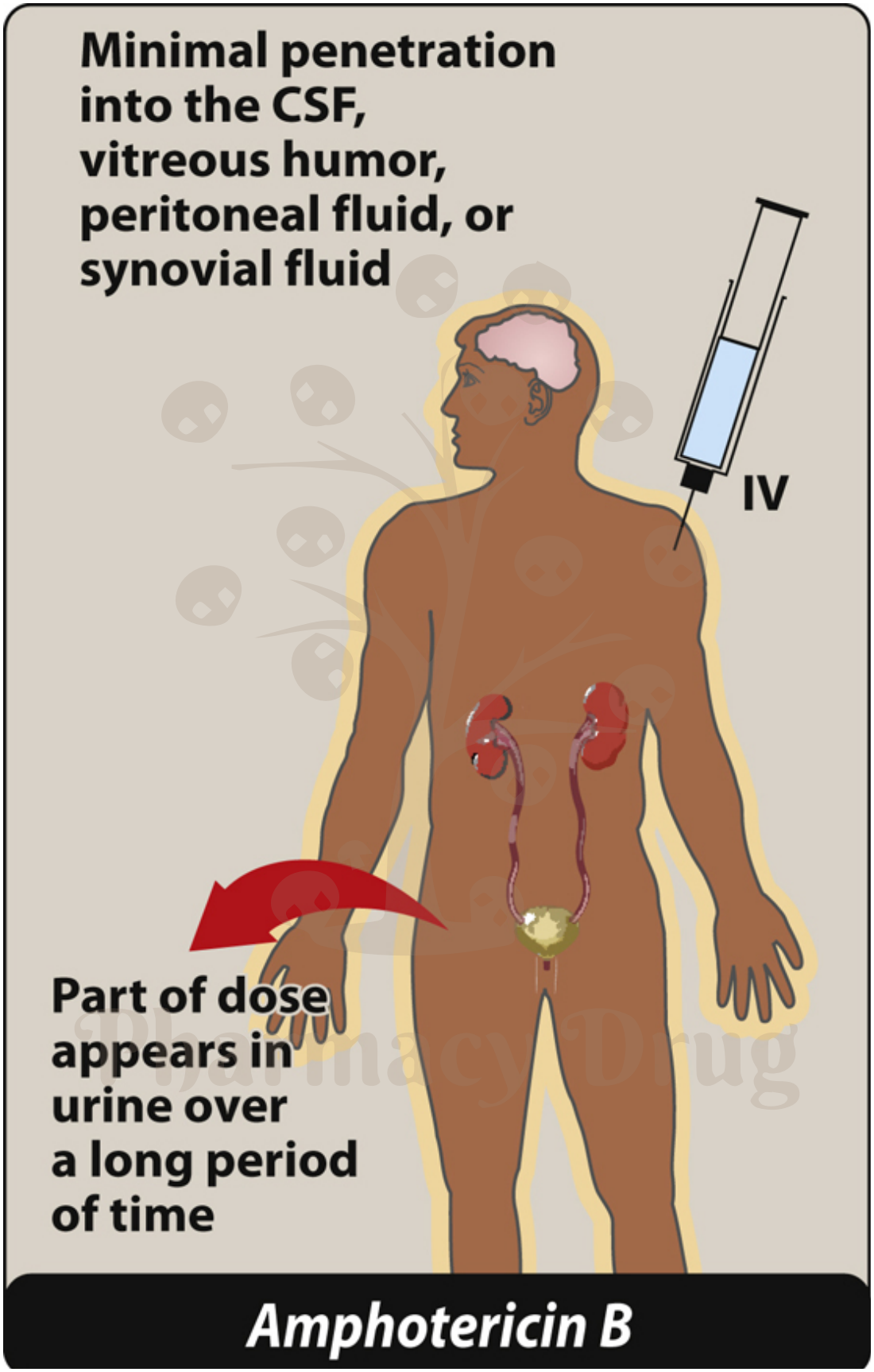

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Figure 33.5 Administration and fate of *amphotericin B*.CSF = cerebrospinal fluid.

5.Adverse effects: *Amphotericin B* has a low therapeutic index. Toxic manifestations are outlined below (Figure 33.6).

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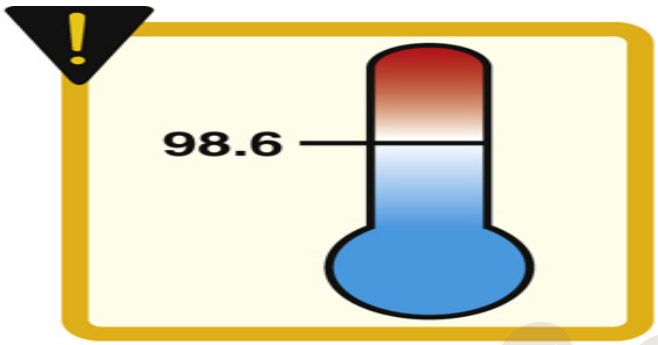
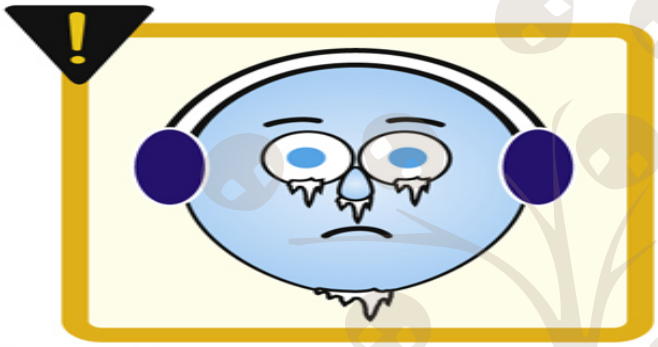


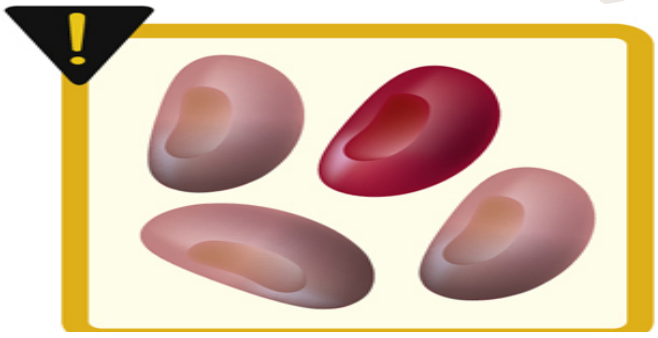
Fever



Chills

Kidney failure

Hypotension



Anemia

Pharmacy Drug

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Figure 33.6 Adverse effects of *amphotericin B*.

a. Fever and chills: These occur most commonly 1 to 3 hours after starting the IV administration but usually subside with repeated administration of the drug. Premedication with a corticosteroid or an antipyretic helps to prevent this problem.

b. Renal impairment: Despite the low levels of the drug excreted in the urine, patients may exhibit a decrease in glomerular filtration rate and renal tubular function. Serum creatinine may increase, creatinine clearance can decrease, and potassium and magnesium are lost. Renal function usually returns with discontinuation of the drug, but residual damage is likely at high doses. Azotemia is exacerbated by other nephrotoxic drugs, such as aminoglycosides, *cyclosporine*, and *vancomycin*, although adequate hydration can decrease its severity. Sodium loading with infusions of normal saline prior to administration of the conventional formulation or use of the liposomal *amphotericin B* products minimizes the risk of nephrotoxicity.

c. Hypotension: A shock-like fall in blood pressure accompanied by hypokalemia may occur, requiring potassium supplementation. Care must be exercised in patients taking *digoxin* and other drugs that can cause potassium fluctuations.

d. Thrombophlebitis: Adding *heparin* to the infusion can alleviate this problem.

B. Antimetabolite antifungals

Flucytosine [floo-SYE-toe-seen] (*5-FC*) is a synthetic pyrimidine antimetabolite that is often used in combination with other

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antifungal agents.

1.Mechanism of action: *5-FC* enters the fungal cell via a cytosine-specific permease, an enzyme not found in mammalian cells. It is subsequently converted to a series of compounds, including *5-fluorouracil* (*5-FU*) and 5-fluorodeoxyuridine 5′-monophosphate, which disrupt nucleic acid and protein synthesis (Figure 33.7). [Note: *Amphotericin B* increases cell permeability, allowing more *5-FC* to penetrate the cell leading to synergistic effects.]

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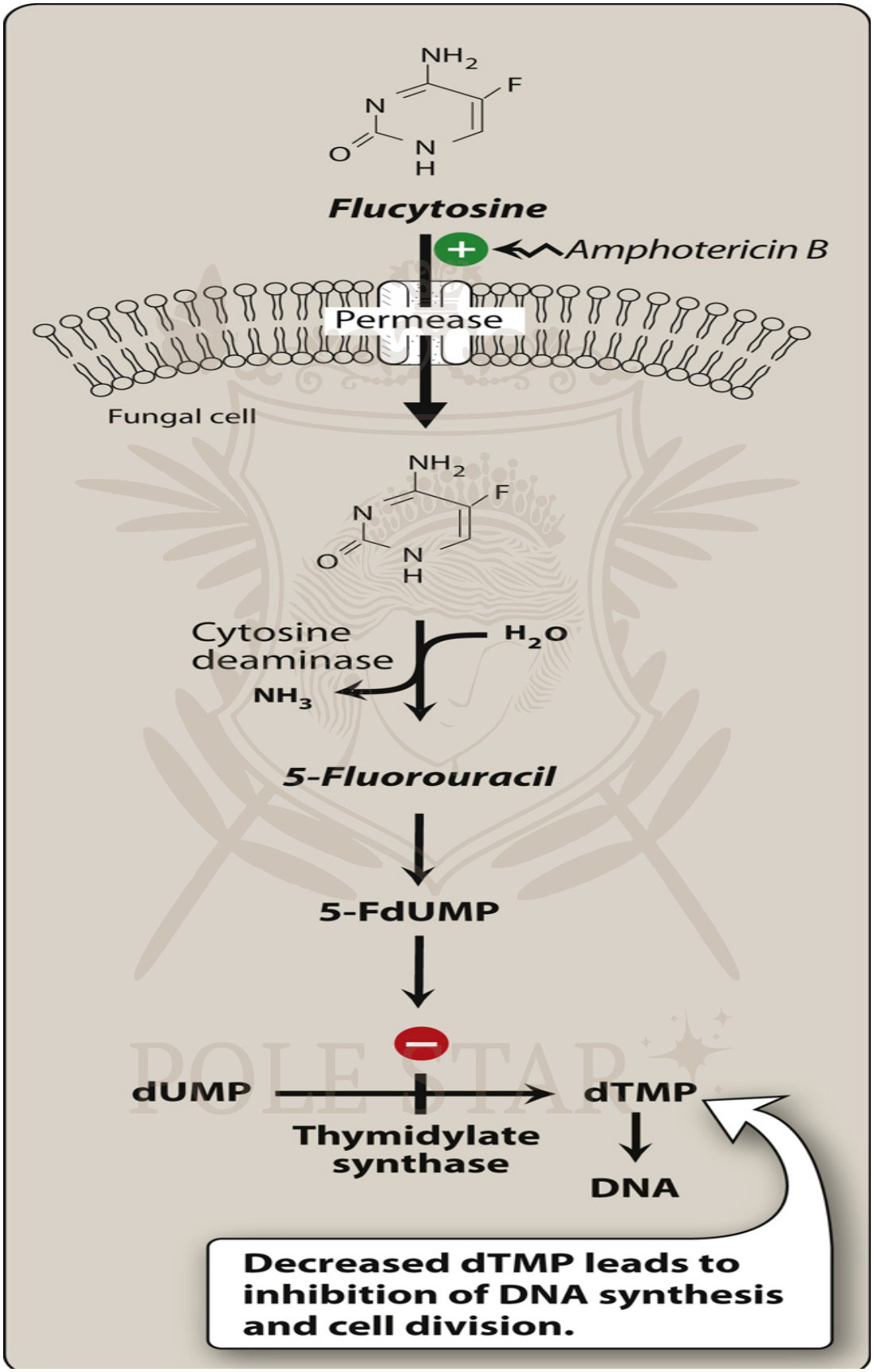
NH2
F
N
O
N
H
Flucytosine
Amphotericin B
Permease
Fungal cell
NH2
F
N
O
N
H
Cytosine deaminase
H2O
NH3
5-Fluorouracil
5-FdUMP
dUMP
dTMP
Thymidylate synthase
DNA
Decreased dTMP leads to inhibition of DNA synthesis and cell division.

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Figure 33.7 Mode of action of *flucytosine*.5-FdUMP = 5-fluorodeoxyuridine 5′-monophosphate; dTMP = deoxythymidine 5′-monophosphate.

2.Antifungal spectrum: *5-FC* is fungistatic. It is effective in combination with *itraconazole* for treating chromoblastomycosis. It is also used in combination with *amphotericin B* for the treatment of systemic mycoses and for meningitis caused by C. neoformans and C. albicans. Flucytosine can also be used for Candida urinary tract infections when *fluconazole* is not appropriate; however, resistance can occur with repeated use.

3.Resistance: Resistance may occur due to decreased levels of any of the enzymes in the conversion of *5-FC* to *5-FU* and other metabolites. The emergence of resistant fungal cells is lower with a combination of *5-FC* plus a second antifungal agent. Thus, *5-FC* is not used as a single antimycotic drug.

4.Pharmacokinetics: *5-FC* is well absorbed after oral administration. It distributes throughout the body water and penetrates well into the CSF. *5-FU* is detectable in patients and is probably the result of metabolism of *5-FC* by intestinal bacteria. Excretion of both the parent drug and metabolites is via glomerular filtration, and the dose must be adjusted in patients with compromised renal function.

5.Adverse effects: *5-FC* causes reversible neutropenia, thrombocytopenia, and dose-related bone marrow depression. Reversible hepatic dysfunction with elevation of serum transaminases has been observed. Nausea, vomiting, and diarrhea are common, and severe enterocolitis may occur.

C. Azole antifungals

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Azole antifungals are made up of two different classes of drugs—imidazoles and triazoles. Although these drugs have similar mechanisms of action and spectra of activity, their pharmacokinetics and therapeutic uses vary significantly. In general, imidazoles are applied topically for cutaneous infections, whereas triazoles are administered systemically for the treatment or prophylaxis of cutaneous and systemic mycoses. [Note: Imidazole antifungals are discussed in the section on agents for cutaneous mycotic infections.] The systemic triazole antifungals include *fluconazole*, *itraconazole*, *posaconazole*, *voriconazole*, and *isavuconazole*.

1.Mechanism of action: Azoles are predominantly fungistatic. They inhibit 14-α-demethylase (a cytochrome P450 [CYP450] enzyme), thereby blocking the demethylation of lanosterol to ergosterol (Figure 33.8). The inhibition of ergosterol biosynthesis disrupts fungal membrane structure and function, which, in turn, inhibits fungal cell growth.

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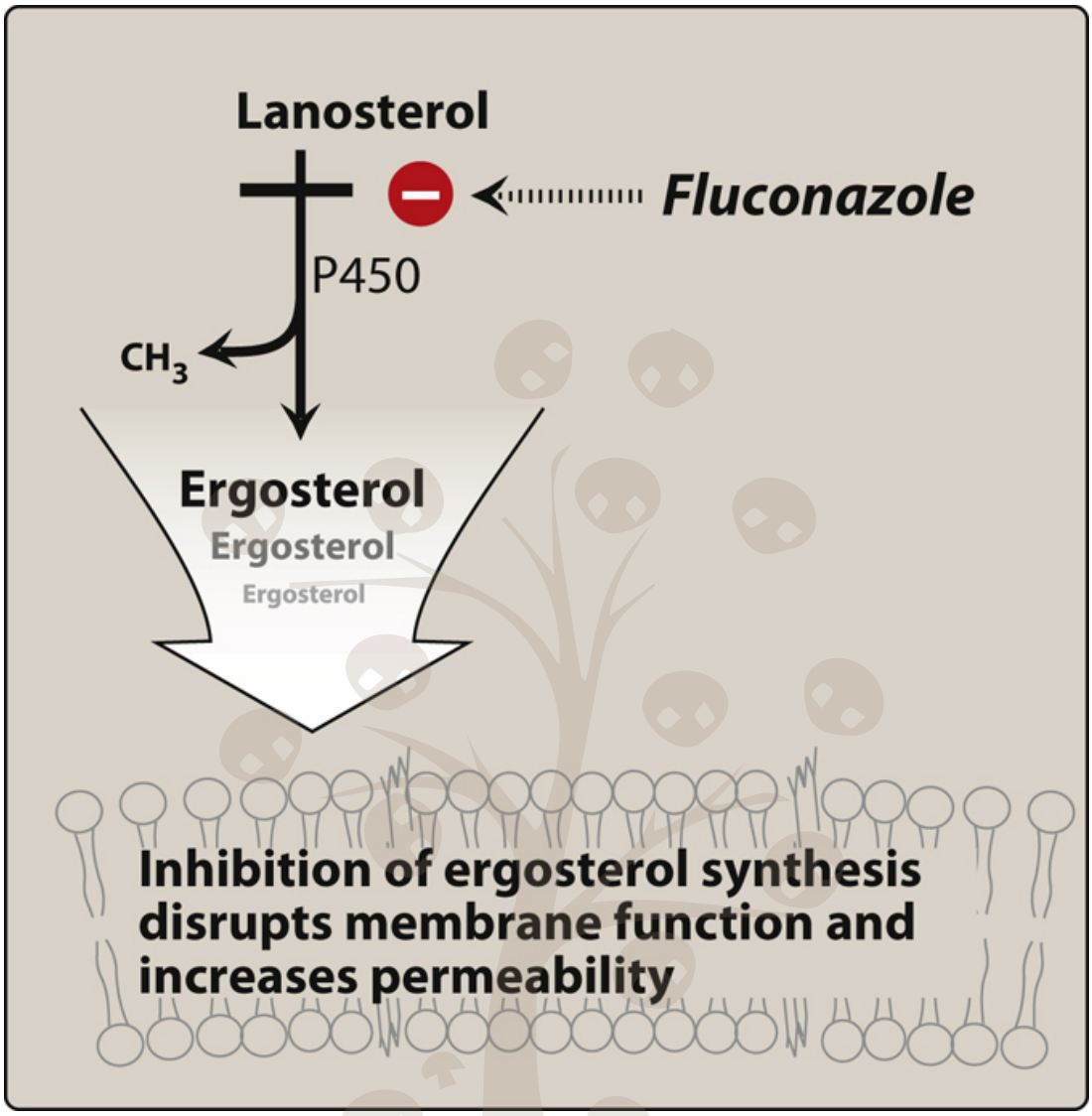

Figure 33.8 Mode of action of azole antifungals.

2.Resistance: Resistance to azole antifungals is becoming a significant clinical problem, particularly with protracted therapy required in immunocompromised patients, such as those who have advanced HIV infection or bone marrow transplant. Mechanisms of resistance include mutations in the 14-α-demethylase gene that lead to decreased azole binding and efficacy. Additionally, some strains of fungi develop efflux pumps that pump the drug out of the cell or have reduced ergosterol in the cell wall.

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Clinical Application 33.1: Development of Resistance to Azole Antifungals

Patients who are immunosuppressed and are on *fluconazole* for long-term prophylaxis, such as patients who have had solid organ or bone marrow transplants, are at higher risk of developing infections with fungal organisms with resistance to the common azoles. These organisms achieve resistance through mutations in the 14-α-demethylase gene, leading to decreased azole binding and reduced efficacy. If a patient on prolonged azole therapy presents with sepsis, suspicion should be high for infections due to azole-resistant fungal organisms. Pending further microbiological workup, including cultures and antifungal susceptibility data, it is preferable to use an antifungal of a different class, such as an echinocandin or *amphotericin B*.

Multiple outbreaks of Candida auris, a Candida species identified as an emerging multidrug-resistant healthcare-associated fungal pathogen, have occurred in healthcare facilities in several countries. This pathogen has shown a higher risk of occurrence in patients with prior antifungal use. It has been especially difficult to treat, given ongoing challenges of organism misidentification and high rates of antifungal drug resistance including some pan-resistant isolates, resulting in significant patient mortality.

3. **Drug interactions:** All azoles inhibit the hepatic CYP3A4 isoenzyme to varying degrees. Patients on concomitant medications that are substrates for this isoenzyme may have increased concentrations and risk for toxicity. Several azoles, including *itraconazole* and *voriconazole*, are metabolized by CYP3A4 and other CYP450 isoenzymes. Therefore, concomitant use of potent CYP450 inhibitors (for example, *ritonavir*) and inducers (for example, *rifampin*, *phenytoin*) can lead to increased adverse effects or clinical failure of these azoles, respectively.

4. **Contraindications:** Azoles are considered teratogenic, and they should be avoided in pregnancy unless the potential benefit outweighs the risk to the fetus.

D. Fluconazole

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Fluconazole [floo-KON-a-zole] was the first triazole antifungal agent. It is the least active of all triazoles, with most of its spectrum limited to yeasts and some dimorphic fungi. It has no role in the treatment of aspergillosis or mucormycosis. It is highly active against C. neoformans and certain species of Candida, including C. albicans and Candida parapsilosis. Resistance is a concern, however, with other species, including Candida krusei and Candida glabrata. *Fluconazole* is used for prophylaxis against invasive fungal infections in recipients of bone marrow transplants. It is the drug of choice for C. neoformans after induction therapy with *amphotericin B* and *flucytosine* and is used for the treatment of candidemia and coccidioidomycosis. *Fluconazole* is effective against most forms of mucocutaneous candidiasis. It is commonly used as a single-dose oral treatment for vulvovaginal candidiasis. *Fluconazole* is available in oral and IV dosage formulations. It is well absorbed after oral administration and distributes widely to body fluids and tissues. The majority of the drug is excreted unchanged via the urine, and doses must be reduced in patients with renal dysfunction. The most common adverse effects with *fluconazole* are nausea, vomiting, headache, and skin rashes.

E. Itraconazole

Itraconazole [it-ra-KON-a-zole] is a synthetic triazole that has a broad antifungal spectrum compared to *fluconazole. Itraconazole* is a drug of choice for the treatment of blastomycosis, sporotrichosis, paracoccidioidomycosis, and histoplasmosis. It is rarely used for the treatment of infections due to Candida and Aspergillus species because of the availability of more effective agents. *Itraconazole* is available as a capsule or oral solution. The capsule should be taken with food, and ideally an acidic beverage, to increase absorption. By contrast, the solution should be taken on an empty stomach, as food decreases the absorption. The drug distributes well in most tissues, including bone and adipose tissues. *Itraconazole* is extensively metabolized by the liver, and the drug and inactive metabolites are excreted in the

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urine and feces. It is a potent inhibitor of CYP3A4 and coadministration of other agents metabolized by CYP3A4 should be avoided, if possible. Adverse effects include nausea, vomiting, diarrhea, rash (especially in immunocompromised patients), hypokalemia, hypertension, edema, and headache. Liver toxicity can also occur, especially when given with other hepatotoxic drugs. *Itraconazole* has a negative inotropic effect and should be avoided in patients with evidence of ventricular dysfunction, such as heart failure.

F. Posaconazole

Posaconazole [poe-sa-KONE-a-zole], a synthetic triazole, is a broad-spectrum antifungal structurally similar to *itraconazole.* It is available as an oral suspension, oral tablet, or IV formulation. *Posaconazole* is commonly used for the treatment and prophylaxis of invasive Candida and Aspergillus infections in severely immunocompromised patients. Because of its broad spectrum of activity, *posaconazole* is used in the treatment of invasive fungal infections caused by Scedosporium and Mucorales. The drug has low oral bioavailability and should be given with food. Unlike other azoles, *posaconazole* is not metabolized by CYP450, but is eliminated via glucuronidation. Drugs that increase gastric pH (for example, proton pump inhibitors) may decrease the absorption of oral *posaconazole* and should be avoided if possible. Due to its potent inhibition of CYP450 3A4, concomitant use of *posaconazole* with a number of agents (for example, ergot alkaloids, *atorvastatin*, *alprazolam*, *citalopram*, and *risperidone*) is contraindicated.

G. Voriconazole

Voriconazole [vor-i-KON-a-zole], a synthetic triazole related to *fluconazole*, is a broad-spectrum antifungal agent that is available in both IV and oral dosage forms. *Voriconazole* has replaced *amphotericin B* as the drug of choice for invasive aspergillosis. It is also approved for the treatment of invasive candidiasis, as well as serious infections caused by Scedosporium and Fusarium

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species. *Voriconazole* has high oral bioavailability and penetrates into tissues well. It is extensively metabolized by CYP2C19, CYP2C9, and CYP3A4 isoenzymes, and the metabolites are primarily excreted via the urine. Inhibitors and inducers of these isoenzymes may impact levels of *voriconazole*, leading to toxicity or clinical failure, respectively. *Voriconazole* displays nonlinear kinetics, which can be affected by drug interactions and pharmacogenetic variability, particularly CYP2C19 polymorphisms. High trough concentrations have been associated with visual and auditory hallucinations and an increased incidence of hepatotoxicity. Other adverse effects include hypokalemia and visual impairment which is usually reversible upon discontinuation of the drug. *Voriconazole* is also an inhibitor of CYP2C19, CYP2C9, and CYP3A4 isoenzymes. Drugs that are substrates of these isoenzymes are impacted by *voriconazole* (Figure 33.9). Because of significant interactions, use of *voriconazole* is contraindicated with many drugs that are inducers of CYP450 (for example, *rifampin*, *rifabutin*, *carbamazepine*, and *St. John's wort*).

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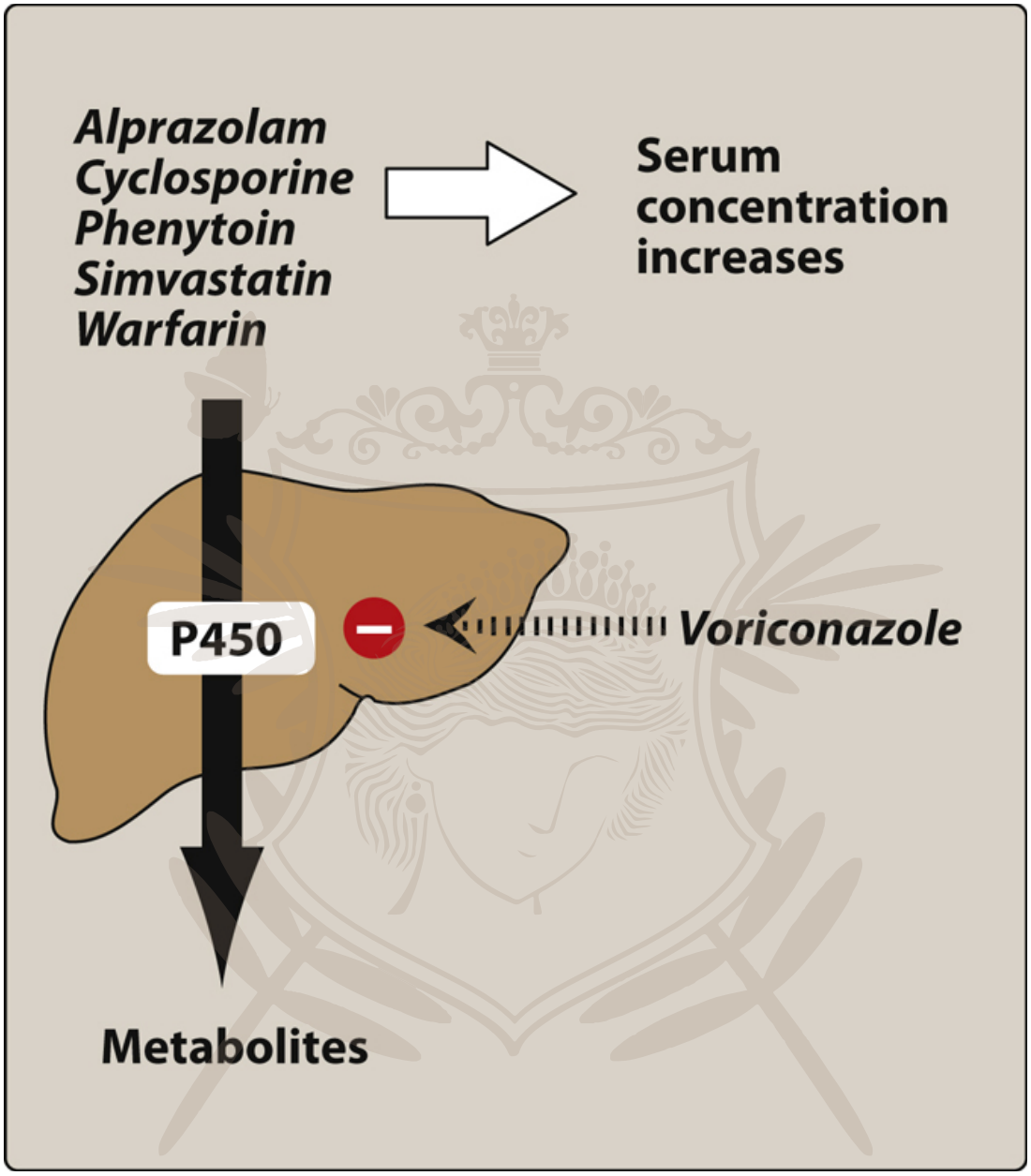

Figure 33.9 By inhibiting cytochrome P450, *voriconazole* can potentiate the toxicities of other drugs.

H. Isavuconazole

Isavuconazole [eye-sa-voo-KON-a-zole] is a broad-spectrum antifungal agent, which is supplied as the prodrug *isavuconazonium* in IV and oral dosage forms. *Isavuconazonium* is rapidly hydrolyzed by esterases in the blood to *isavuconazole.*

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Isavuconazole has a spectrum of activity similar to *voriconazole* and is approved for invasive aspergillosis and invasive mucormycosis. *Isavuconazonium* has high bioavailability after oral administration and distributes well into tissues. The drug is metabolized by CYP3A4, CYP3A5, and uridine diphosphate-glucuronosyltransferases. Coadministration of *isavuconazole* with potent CYP3A4 inhibitors and inducers is contraindicated. *Isavuconazole* is also an inhibitor of the CYP3A4 isoenzyme, thereby increasing the concentrations of drugs that are substrates of CYP3A4. Nausea, vomiting, diarrhea, and hypokalemia are common adverse effects.

Figures 33.10 and 33.11 summarize the azole antifungal agents.

	Fluconazole	*Itraconazole*	*Isavuconazole*	*Voriconazole*	*Posaconazole*
Spectrum of activity	+	++	+++	+++	++++
Route(s) of administration	Oral, IV	Oral	Oral, IV	Oral, IV	Oral, IV
Oral bioavailability (%)	95	55 (solution)	98	96	Variable
Drug levels affected by food or gastric pH	No	Yes	No	No	Yes
Protein binding (%)	10	99	99	58	99
Primary route of elimination	Renal	Hepatic CYP3A4	Hepatic CYP3A4, UGT	Hepatic CYP2C19, 2C9, 3A4	Hepatic glucuronidation
Cytochrome P450 enzymes inhibited	CYP3A4, 2C9, 2C19	CYP3A4	CYP3A4	CYP2C19, 2C9, 3A4	CYP3A4
Half-life ($t_{1/2}$)	25 h	30–40 h	130 h	Dose dependent	20–66 h
CSF penetration	Yes	No	Yes	Yes	Yes
Renal excretion of active drug (%)	>90	<2	45	<2	<2
TDM recommended (rationale)	No	Yes (efficacy)	No	Yes (efficacy and safety)	Yes (efficacy)

Figure 33.10 Summary of triazole antifungals.CSF = cerebrospinal fluid; TDM = therapeutic drug monitoring.

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INTERACTING DRUG	AZOLE DRUG	EFFECT ON DRUG EXPOSURE	MAIN CLINICAL CONSEQUENCE OF INTERACTION
Amiodarone, dronedarone, citalopram, pimozide, quinidine	*Isavuconazole, itraconazole, fluconazole, voriconazole, posaconazole**	↑ Exposure to interacting drugs	QT interval prolongation with risk of torsades de pointes
Carbamazepine	*Isavuconazole, voriconazole*	↓ Exposure to *voriconazole*	Treatment failure of *voriconazole*
Efavirenz	*Isavuconazole, voriconazole*	↓ Exposure to *voriconazole*	Treatment failure of *voriconazole*
		↑ Exposure to *efavirenz*	Risk of *efavirenz* toxicity
Ergot alkaloids	*Isavuconazole, itraconazole, fluconazole, voriconazole, posaconazole**	↑ Exposure to ergot alkaloid	Ergotism
Lovastatin, simvastatin	*Itraconazole, voriconazole, posaconazole*	↑ Exposure to HMG-CoA reductase inhibitor	Risk of rhabdomyolysis
Midazolam, triazolam, alprazolam	*Isavuconazole, itraconazole, voriconazole, posaconazole*	↑ Exposure to benzodiazepine	Excessive sedation
Phenytoin	*Isavuconazole, voriconazole, posaconazole*	↓ Exposure to *voriconazole, posaconazole*	Treatment failure
		↑ Exposure to *phenytoin*	Nystagmus, ataxia
Rifabutin	*Isavuconazole, voriconazole, posaconazole*	↓ Exposure to *voriconazole*	Treatment failure of *voriconazole*
		↑ Exposure to *rifabutin*	Uveitis
Rifampicin (rifampin)	*Isavuconazole, voriconazole, posaconazole*	↓ Exposure to *voriconazole*	Treatment failure of *voriconazole*
Ritonavir	*Isavuconazole, voriconazole*	↓ Exposure to *voriconazole*	Treatment failure of *voriconazole*
Vincristine, vinblastine	*Isavuconazole, itraconazole, voriconazole, posaconazole*	↑ Exposure to vinca alkaloids	Neurotoxicity
Sirolimus	*Isavuconazole, voriconazole, posaconazole*	↑ Exposure to *sirolimus*	Risk of *sirolimus* toxicity

Figure 33.11 Major or life-threatening drug interactions of azole drugs.↑ indicates increased; ↓ indicates decreased. *Where an interaction has been reported for one triazole, the contraindication has been extended to all others.Modified from Springer Nature: Y.Nivoix , D.Leveque , and R.Herbrecht , et al. The enzymatic basis of drug-drug interactions with systemic triazole antifungals. *Clin. Pharmacokinet*. 47: 779 (2008).

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Clinical Application 33.2: Prolongation of the QT Interval Due to Azole Antifungal Agents

Azoles can lead to a long QT interval on a patient's electrocardiogram. Long QT interval can lead to a type of ventricular tachycardia called torsades de pointes. Torsades de pointes can be self-terminating, causing dizzy spells and syncope, or it can degenerate into ventricular fibrillation, cardiac arrest, and sudden cardiac death. Given the potential for fatality, patients should have a baseline

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electrocardiogram before the start of systemic azole therapy, especially when high doses are used. The current drug regimen should also be evaluated for concomitant medications that are associated with QT prolongation and torsades de pointes and also for drugs causing pharmacokinetic interactions that may lead to increased drug exposure. Patients at higher risk or those with high baseline QT intervals may need closer monitoring of the electrocardiogram while on azole therapy. Unlike other azoles, *isavuconazole* has been associated with shortening of the QT interval. Therefore, it may be an alternative when azole treatment is required in a patient with a high baseline QT interval.

I. Echinocandins

Echinocandins interfere with the synthesis of the fungal cell wall by inhibiting the synthesis of β(1,3)-d-glucan, leading to lysis and cell death. *Caspofungin*, *micafungin*, and *anidulafungin* are available for IV administration once daily. *Micafungin* is the only echinocandin that does not require a loading dose. The echinocandins have potent activity against Aspergillus and most Candida species, including those species resistant to azoles. However, they have minimal activity against other fungi. The most common adverse effects are fever, rash, nausea, and phlebitis at the infusion site. They should be administered via a slow IV infusion, as they can cause a histamine-like reaction (flushing) when infused rapidly.

1.Caspofungin: *Caspofungin* [kas-poh-FUN-jin] is a first-line option for patients with invasive candidiasis, including candidemia, and a second-line option for invasive aspergillosis in patients who have failed or cannot tolerate *amphotericin B* or an azole. The dose of *caspofungin* should be adjusted with moderate hepatic dysfunction. Concomitant administration of *caspofungin* with CYP450 enzyme inducers (for example, *rifampin*, *carbamazepine*, *phenytoin*) may require an increase in *caspofungin* dose. *Caspofungin* should not be coadministered with *cyclosporine* due to a high incidence of elevated hepatic transaminases with concurrent use.

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2.Micafungin and anidulafungin: *Micafungin* [mi-ka-FUN-jin] and *anidulafungin* [ay-nid-yoo-la-FUN-jin] are first-line options for the treatment of invasive candidiasis, including candidemia. *Micafungin* is also indicated for the prophylaxis of invasive Candida infections in patients who are undergoing hematopoietic stem cell transplantation. These agents are not substrates for CYP450 enzymes and do not have any associated drug interactions.

III. DRUGS FOR CUTANEOUS MYCOTIC INFECTIONS

Mold-like fungi that cause cutaneous infections are called dermatophytes or tinea. Tinea infections are classified by the affected site (for example, tinea pedis, which refers to an infection of the feet). Common dermatomycoses, such as tinea infections that appear as rings or round red patches with clear centers, are often referred to as “ringworm.” This is a misnomer because fungi rather than worms cause the disease. The three different fungi that cause the majority of cutaneous infections are Trichophyton, Microsporum, and Epidermophyton. The yeasts Malassezia and Candida may also cause infections of the skin. The drugs used in the treatment of cutaneous mycoses are listed in Figure 33.1.

A. Squalene epoxidase inhibitors

These agents act by inhibiting squalene epoxidase, thereby blocking the biosynthesis of ergosterol, an essential component of the fungal cell membrane (Figure 33.12). Accumulation of toxic amounts of squalene results in increased membrane permeability and death of the fungal cell.

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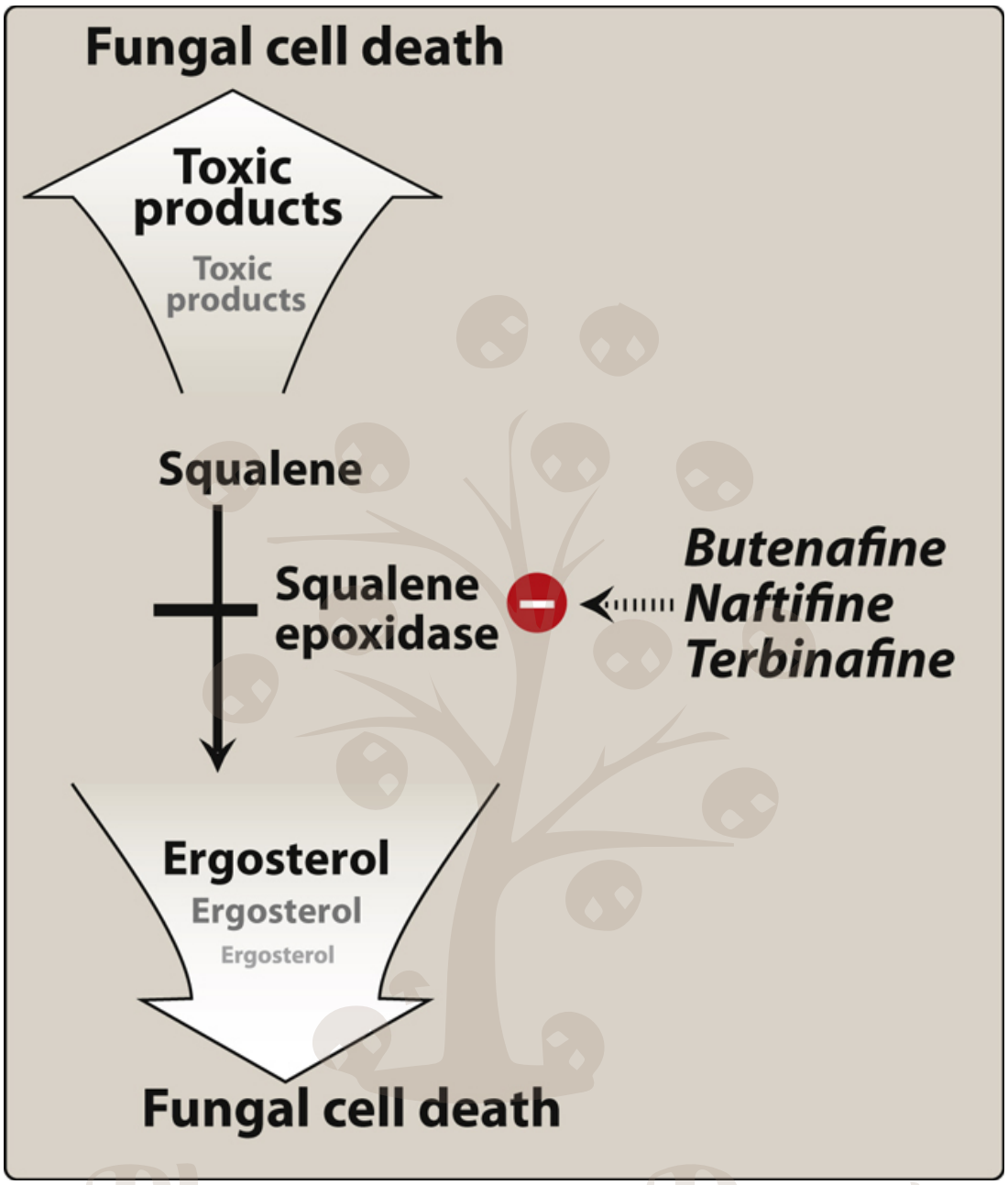

Figure 33.12 Mode of action of squalene epoxidase inhibitors.

1. Terbinafine: Oral *terbinafine* [TER-bin-a-feen] is the drug of choice for treating dermatophyte onychomycoses (fungal infections of nails). It is better tolerated, requires a shorter duration of therapy, and is more effective than either *itraconazole* or *griseofulvin* for Trichophyton. Therapy is

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prolonged (usually about 3 months) but considerably shorter than that with *griseofulvin* and topical antifungals. Oral *terbinafine* may also be used for tinea capitis (infection of the scalp). [Note: Oral antifungal therapy (*griseofulvin*, *terbinafine*, *itraconazole*) is needed for tinea capitis. Topical antifungals are ineffective.] Topical *terbinafine* (1% cream, gel or solution) is used to treat tinea pedis, tinea corporis (ringworm), tinea cruris (infection of the groin or "jock itch"), and tinea versicolor due to Malassezia furfur. Duration of treatment is usually 1 week.

a. Antifungal spectrum: *Terbinafine* is active against Trichophyton and Malassezia. It may also be effective against Candida, Epidermophyton, and Scopulariopsis, but the efficacy in treating clinical infections due to these pathogens has not been established.

b. Pharmacokinetics: *Terbinafine* is available for oral and topical administration. The bioavailability after oral administration is only 40% due to first-pass metabolism. *Terbinafine* is highly protein bound and is deposited in the skin, nails, and adipose tissue. A prolonged terminal half-life of 200 to 400 hours may reflect the slow release from these tissues. Oral *terbinafine* is extensively metabolized by several CYP450 isoenzymes and is excreted mainly via the urine (Figure 33.13). The drug should be avoided in patients with moderate to severe renal impairment or hepatic dysfunction. *Terbinafine* is an inhibitor of the CYP2D6 isoenzyme, and concomitant use with substrates of CYP2D6 may result in an increased risk of adverse effects with those agents.

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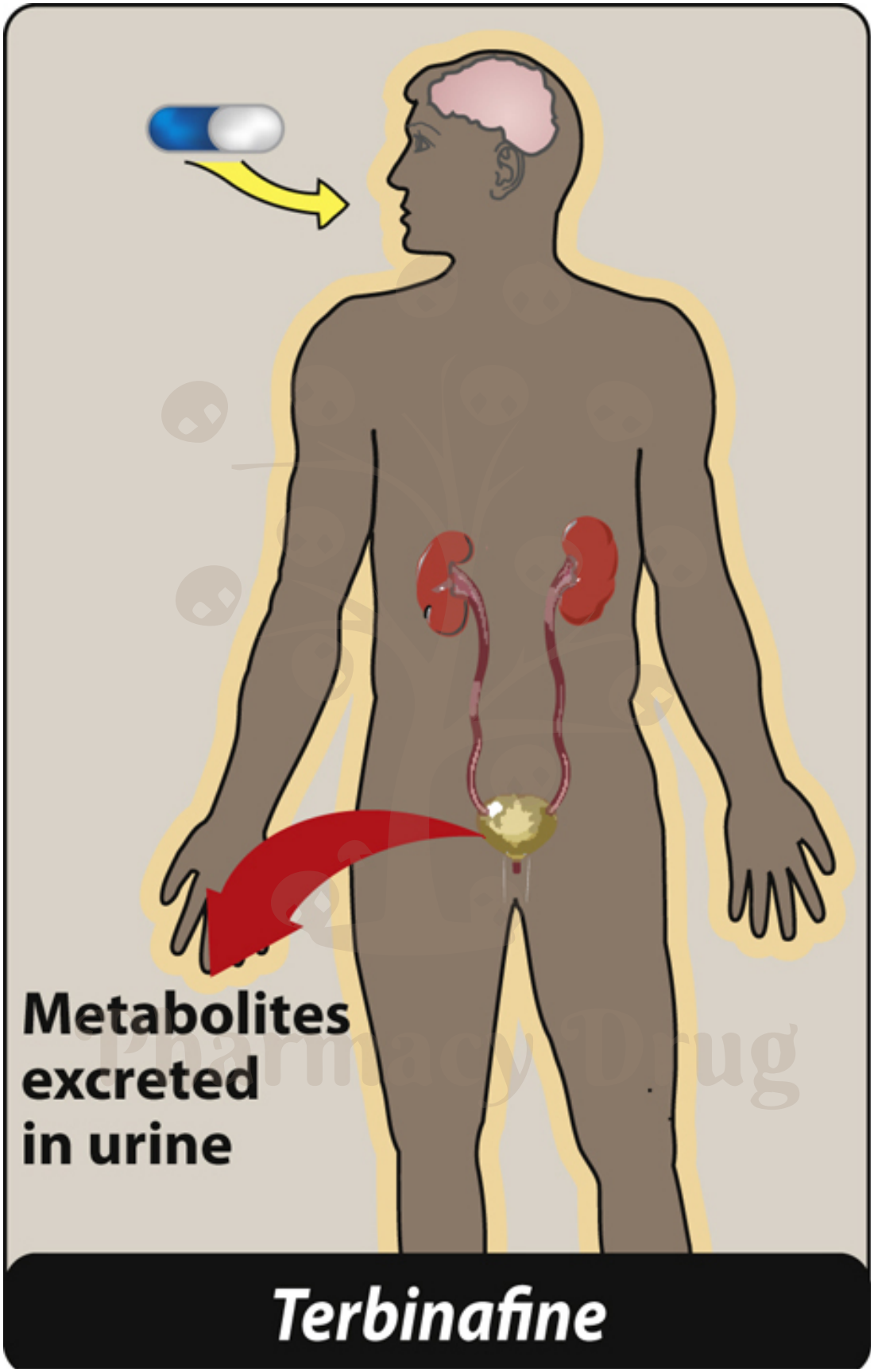

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Figure 33.13 Administration and fate of *terbinafine*.

c. Adverse effects: Common adverse effects with the oral formulation include diarrhea, dyspepsia, nausea, headache, and rash. Taste and visual disturbances have been reported, as well as elevations in serum hepatic transaminases. The topical formulations are well tolerated.

2. Naftifine: *Naftifine* [NAF-ti-feen] is active against Trichophyton, Microsporum, and Epidermophyton. *Naftifine* cream and gel are used for the topical treatment of tinea corporis, tinea cruris, and tinea pedis. Duration of treatment is usually 2 to 4 weeks.

3. Butenafine: *Butenafine* [byoo-TEN-a-feen] is active against Trichophyton rubrum, Epidermophyton, and Malassezia. Like *naftifine*, *butenafine* cream is used for the topical treatment of tinea infections.

B. Griseofulvin

Griseofulvin [gris-ee-oh-FUL-vin] causes disruption of the mitotic spindle and inhibition of fungal mitosis (Figure 33.14). It has been largely replaced by oral *terbinafine* for the treatment of onychomycosis, although it is still used for dermatophytosis of the scalp and hair. *Griseofulvin* is fungistatic and requires a long duration of treatment (for example, 6-12 months for onychomycosis). Duration of therapy is dependent on the rate of replacement of healthy skin and nails. Ultrafine crystalline preparations are absorbed adequately from the gastrointestinal tract, and absorption is enhanced by high-fat meals. The drug concentrates in the skin, hair, nails, and adipose tissue. *Griseofulvin* induces hepatic CYP450 activity, which increases the rate of metabolism of a number of drugs, including anticoagulants. The use of *griseofulvin* is contraindicated in pregnancy and patients with porphyria.

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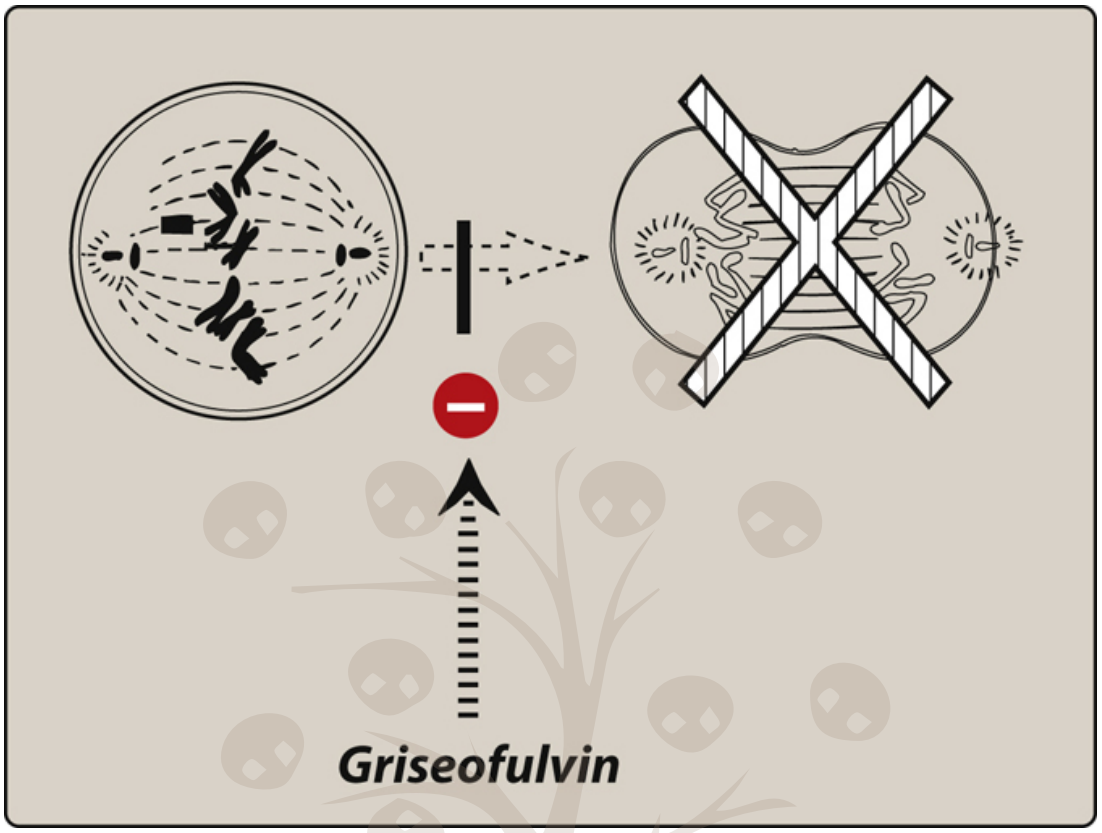

Figure 33.14 Inhibition of mitosis by *griseofulvin*.

C. Nystatin

Nystatin [nye-STAT-in] is a polyene antifungal, and its structure, chemistry, mechanism of action, and resistance profile resemble those of *amphotericin B.* It is used for the treatment of cutaneous and oral Candida infections. The drug is negligibly absorbed from the gastrointestinal tract, and it is not used parenterally due to systemic toxicity (acute infusion-related adverse effects and nephrotoxicity). It is administered as an oral agent ("swish and swallow" or "swish and spit") for the treatment of oropharyngeal candidiasis (thrush), intravaginally for vulvovaginal candidiasis, or topically for cutaneous candidiasis.

D. Imidazoles

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Imidazoles are azole derivatives, which currently include *butoconazole* [byoo-toe-KON-a-zole], *clotrimazole* [kloe-TRIM-a-zole], *econazole* [ee-KON-a-zole], *ketoconazole* [kee-toe-KON-a-zole], *miconazole* [my-KON-a-zole], *oxiconazole* [oks-i-KON-a-zole], *sertaconazole* [ser-ta-KON-a-zole], *sulconazole* [sul-KON-a-zole], *terconazole* [ter-KON-a-zole], and *tioconazole* [tee-oh-KON-a-zole]. As a class of topical agents, they have a wide range of activity against Epidermophyton, Microsporum, Trichophyton, Candida, and Malassezia, depending on the agent. The topical imidazoles have a variety of uses, including tinea corporis, tinea cruris, tinea pedis, and oropharyngeal and vulvovaginal candidiasis. Topical use is associated with contact dermatitis, vulvar irritation (with vaginal preparations), and edema. *Clotrimazole* is also available as a troche (lozenge), and *miconazole* is available as a buccal tablet for the treatment of thrush. Oral *ketoconazole* is rarely used today due to the risk of severe liver injury, adrenal insufficiency, and adverse drug interactions. Topical formulations of *ketoconazole* are useful in the treatment of tinea versicolor and seborrheic dermatitis.

E. Efinaconazole

Efinaconazole [eff-in-a-KON-a-zole] is a topical triazole antifungal agent approved for the treatment of toenail onychomycosis caused by T. rubrum and Trichophyton mentagrophytes. The duration of treatment is 48 weeks.

F. Ciclopirox

Ciclopirox [sye-kloe-PEER-oks], a pyridine antimycotic, inhibits the transport of essential elements in the fungal cell, disrupting the synthesis of DNA, RNA, and proteins. *Ciclopirox* is active against Trichophyton, Epidermophyton, Microsporum, Candida, and Malassezia. It is available in a number of formulations. *Ciclopirox* shampoo is used for the treatment of seborrheic dermatitis. Tinea pedis, tinea corporis, tinea cruris, cutaneous candidiasis, and tinea versicolor may be treated with the cream,

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gel, or suspension. Onychomycosis can be treated with the nail lacquer formulation.

G. Tavaborole

Tavaborole [tav-a-BOOR-ole] inhibits an aminoacyl-transfer ribonucleic acid synthetase, preventing fungal protein synthesis. *Tavaborole* is active against T. rubrum and T. mentagrophytes. It is available as a topical solution for the treatment of toenail onychomycosis, requiring 48 weeks of treatment.

H. Tolnaftate

Tolnaftate [tole-NAF-tate], a topical thiocarbamate, distorts the hyphae and stunts mycelial growth in susceptible fungi. *Tolnaftate* is active against Epidermophyton, Microsporum, and Malassezia furfur. [Note: *Tolnaftate* is not effective against Candida.] *Tolnaftate* is used to treat tinea pedis, tinea cruris, and tinea corporis. It is available as a solution, cream, and powder.

Chapter Summary

- Cutaneous fungal infections, such as tinea corporis and tinea pedis, are often treated with topical antifungal agents. Subcutaneous or systemic fungal infections require treatment with oral or IV antifungal agents.
- *Amphotericin B* is available in IV formulation only and is an optional therapy for some life-threatening fungal infections. Its major adverse effects include fever and chills, renal impairment, and hypotension.
- *Flucytosine* given in combination with *amphotericin B* is the preferred initial treatment for meningitis caused by *C. neoformans.* Resistance to *flucytosine* develops if it is not administered with another antifungal drug.
- Azole antifungals inhibit 14-α-demethylase, blocking the conversion of lanosterol to ergosterol. Azoles are grouped into imidazoles, which are topical agents, and triazoles, which are generally systemic antifungal drugs.
- Azoles inhibit the CYP3A4 isoenzyme, which can lead to an increase in levels of other drugs and potential toxicity. Some azoles, such as *voriconazole* and *isavuconazole*, are metabolized by CYP450 enzymes, and drug interactions with these enzymes could cause toxicity or clinical failure.

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- Echinocandins stop the formation of the fungal cell wall by inhibiting β(1,3)-d-glucan. All echinocandins are available in IV formulation only, and they are overall well tolerated.
- Oral *terbinafine* is the drug of choice for onychomycosis. *Terbinafine* is metabolized by CYP450 enzymes and inhibits CYP2D6. *Terbinafine* is contraindicated in patients with hepatic dysfunction or moderate to severe renal impairment.
- *Efinaconazole*, *ciclopirox*, and *tavaborole* are topical agents for the treatment of onychomycosis. The duration of treatment for these infections is long, up to 48 weeks.

STUDY QUESTIONS

Choose the ONE best answer.

33.1 Which of the following antifungal agents is MOST likely to cause renal insufficiency?

A. Fluconazole
B. Amphotericin B
C. Itraconazole
D. Posaconazole

Correct answer = B. Amphotericin B is the best choice since nephrotoxicity is commonly associated with this medication. Although the dose of fluconazole must be adjusted for renal insufficiency, it is not associated with causing nephrotoxicity. Itraconazole and posaconazole are metabolized by the liver and are not associated with nephrotoxicity.

33.2 Which of the following drugs works by creating pores/channels in the fungal cell membrane?

A. Fluconazole
B. Anidulafungin
C. Amphotericin B
D. Flucytosine

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Correct answer = C. Amphotericin B creates pores/channels in the fungal cell membrane. Fluconazole works by inhibiting the conversion of lanosterol to ergosterol. Anidulafungin inhibits the synthesis of β-d-glucan. Flucytosine disrupts nucleic acid and protein synthesis.

33.3 A patient with a new diagnosis of HIV presents with headache and is found to have cryptococcal meningitis. He is started on an appropriate therapy and a few weeks later he is noted to have bone marrow suppression with pancytopenia. Which of the following antifungals is MOST likely to have caused bone marrow suppression in this patient?

A. Amphotericin B
B. Fluconazole
C. Flucytosine
D. Micafungin

Correct answer = C. Flucytosine causes reversible neutropenia and thrombocytopenia and counts should be monitored while on therapy.

33.4 A 55-year-old woman presents to the hospital with shortness of breath, fever, and malaise. She has a history of breast cancer and is receiving chemotherapy. Her chest X-ray shows pneumonia, and respiratory cultures are positive for Aspergillus fumigatus. Which of the following is the MOST appropriate choice for treatment?

A. Voriconazole
B. Fluconazole
C. Flucytosine
D. Ketoconazole

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Correct answer = A. Voriconazole is the drug of choice for aspergillosis. Studies have found it to be superior to other regimens including amphotericin B. Fluconazole, flucytosine, and ketoconazole do not have reliable in vitro activity and are therefore not recommended.

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33.5 A 22-year-old woman reports a cottage cheese–like vaginal discharge and slight dysuria for 1 week. The patient is diagnosed with vulvovaginal candidiasis. She requests as short a course of treatment as possible due to her busy schedule. Which of the following antifungals is the best choice?

A. Oral fluconazole
B. Topical miconazole
C. Oral terbinafine
D. Topical efinaconazole

Correct answer = A. Oral fluconazole can be given as a one-time dose for vulvovaginal candidiasis. Topical miconazole requires multiple days of therapy. Terbinafine and efinaconazole are not used clinically for vulvovaginal candidiasis.

33.6 A patient will need to receive an azole long-term as suppressive antifungal therapy. At the latest clinic visit, his renal function had declined (calculated Cockcroft-Gault 35 mL/min). Which of the following azoles would need to have a dose reduction due to the patient's renal function?

A. Fluconazole
B. Itraconazole
C. Isavuconazole
D. Posaconazole

Correct answer = A. Fluconazole is the only azole that requires dose adjustment in renal impairment.

POLE STAR

33.7 A 27-year-old man is newly diagnosed with HIV infection and presents with mild oropharyngeal candidiasis (thrush). He denies having dysphagia (difficulty swallowing) or odynophagia (pain from swallowing). Which of the following is the best treatment recommendation for this patient?

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A. Flucytosine capsules
B. Clotrimazole troches
C. Amphotericin B intravenous
D. Voriconazole intravenous

Correct answer = B. Clotrimazole troches are a first-line option for treatment of thrush. Since the patient has a mild infection and does not have any dysphagia, an intravenous option is not needed. Flucytosine is not used for thrush.

33.8 Which of the following drugs is relatively free of drug–drug interactions?

A. Voriconazole
B. Itraconazole
C. Anidulafungin
D. Terbinafine

Correct answer = C. The echinocandins (including anidulafungin) are not metabolized by the CYP450 enzyme system, so they have very few drug–drug interactions. Voriconazole, itraconazole, and terbinafine are all metabolized by the CYP450 enzyme system, so they have significant drug–drug interactions.

33.9 A 56-year-old woman with diabetes complains of thickening of the nail of the right big toe and a change in color (yellow). The podiatrist diagnoses the patient with onychomycosis of the toenails. Which of the following is the most appropriate choice for treating this infection?

A. Terbinafine
B. Micafungin
C. Itraconazole
D. Griseofulvin

Correct answer = A. Terbinafine is better tolerated, requires a shorter duration of therapy, and is more effective than either itraconazole or griseofulvin. Micafungin is not active for this type of infection.

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33.10 A patient is diagnosed with tinea pedis. He does not have any contraindications to potential therapies. Which of the following drugs should be recommended?

A. Terbinafine tablets
B. Fluconazole tablets
C. Naftifine topical cream
D. Tavaborole topical solution

Correct answer = C. Naftifine topical cream is effective against tinea pedis. Systemic therapy (oral terbinafine or fluconazole) is not needed. Tavaborole topical solution is only indicated for onychomycosis, not tinea pedis.

POLE STAR

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34

Antiviral Drugs

Elizabeth Sherman

I. OVERVIEW

Viruses are obligate intracellular parasites. They lack both a cell wall and a cell membrane, and they do not carry out metabolic processes. Viruses use much of the metabolic machinery of the host, and few drugs are selective enough to prevent viral replication without injury to the infected host cells. Therapy for viral diseases is further complicated by the fact that clinical symptoms appear late in the course of the disease, at a time when most of the virus particles have replicated. At this stage of viral infection, administration of drugs that block viral replication has limited effectiveness in many cases. However, a few virus groups respond to available antiviral drugs, and some antiviral agents are useful as prophylactic agents. These agents are discussed in this chapter. To assist in the review of these drugs, they are grouped according to the type of viral infection they target (Figure 34.1).

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FOR RESPIRATORY VIRUS INFECTIONS

Amantadine GENERIC ONLY
Baloxavir XOFLUZA
Oseltamivir TAMIFLU
Peramivir RAPIVAB
Remdesivir VEKLURY
Ribavirin VIRAZOLE
Rimantadine FLUMADINE
Zanamivir RELENZA

FOR HEPATIC VIRAL INFECTIONS: HEPATITIS B

Adefovir HEPSERA
Entecavir BARACLUDE
Lamivudine EPIVIR-HBV
Peginterferon alfa-2a PEGASYS

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Tenofovir alafenamide VEMLIDY
Tenofovir disoproxil fumarate VIREAD

FOR HEPATIC VIRAL INFECTIONS: HEPATITIS C

Elbasvir/grazoprevir ZEPATIER
Glecaprevir/pibrentasvir MAVYRET
Ledipasvir/sofosbuvir HARVONI
Ribavirin REBETOL
Sofosbuvir SOVALDI
Sofosbuvir/velpatasvir EPCLUSA
Sofosbuvir/velpatasvir/voxilaprevir VOSEVI

FOR HERPESVIRUS AND CYTOMEGALOVIRUS INFECTIONS

Acyclovir ZOVIRAX
Cidofovir GENERIC ONLY
Famciclovir GENERIC ONLY
Foscarnet FOSCAVIR
Ganciclovir CYTOVENE
Penciclovir DENAVIR
Trifluridine VIROPTIC
Valacyclovir VALTREX
Valganciclovir VALCYTE

FOR HIV: NUCLEOSIDE AND NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS

Abacavir ZIAGEN
Didanosine VIDEX
Emtricitabine EMTRIVA
Lamivudine EPIVIR
*Tenofovir alafenamide**
Tenofovir disoproxil fumarate VIREAD
Zidovudine RETROVIR

FOR HIV: NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Doravirine PIFELTRO
Efavirenz SUSTIVA
Etravirine INTELENCE
Nevirapine VIRAMUNE
Rilpivirine EDURANT

FOR HIV: PROTEASE INHIBITORS

Atazanavir REYATAZ
Darunavir PREZISTA
Fosamprenavir LEXIVA

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Lopinavir/ritonavir KALETRA
Nelfinavir VIRACEPT
Saquinavir INVIRASE
Tipranavir APTIVUS

FOR HIV: ENTRY INHIBITORS

Enfuvirtide FUZEON
Fostemsavir RUKOBIA
Ibalizumab TROGARZO
Maraviroc SELZENTRY

FOR HIV: INTEGRASE INHIBITORS

*Bictegravir**
Cabotegravir APRETUDE, VOCABRIA
Dolutegravir TIVICAY
*Elvitegravir**
Raltegravir ISENTRESS

FOR HIV: PHARMACOKINETIC ENHANCERS

Cobicistat TYBOST
Ritonavir NORVIR

POLE STAR

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FOR HIV: FIXED-DOSE COMBINATIONS

Abacavir + lamivudine EPZICOM

Abacavir + lamivudine + dolutegravir TRIUMEQ

Abacavir + zidovudine + lamivudine TRIZIVIR

Bictegravir + tenofovir alafenamide + emtricitabine BIKTARVY

Efavirenz + emtricitabine + tenofovir disoproxil fumarate ATRIPLA

Elvitegravir + cobicistat + tenofovir alafenamide + emtricitabine GENVOYA

Elvitegravir + cobicistat + tenofovir disoproxil fumarate + emtricitabine STRIBILD

Emtricitabine + tenofovir alafenamide DESCOVY

Emtricitabine + tenofovir disoproxil fumarate TRUVADA

Rilpivirine + tenofovir alafenamide + emtricitabine ODEFSEY

Rilpivirine + tenofovir disoproxil fumarate + emtricitabine COMPLERA

Zidovudine + lamivudine COMBIVIR

@Pharmacy_Z

Figure 34.1 Summary of antiviral drugs.HIV = human immunodeficiency virus. *Part of a fixed-dose combination.

II. TREATMENT OF RESPIRATORY VIRAL INFECTIONS

Viral respiratory tract infections for which treatments exist include influenza A and B, respiratory syncytial virus (RSV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, COVID-19). [Note: Immunization against influenza and COVID-19 is the preferred approach. However, antiviral agents are used when patients are allergic to the vaccine (influenza) or outbreaks occur.]

A. Neuraminidase inhibitors

The neuraminidase inhibitors *oseltamivir* [os-el-TAM-i-veer], *zanamivir* [za-NA-mi-veer], and *peramivir* [pe-RA-mi-veer] are effective against both type A and type B influenza viruses. They do not interfere with the immune response to influenza vaccine. Administered prior to exposure, neuraminidase inhibitors prevent infection and, when administered within 24 to 48 hours after the onset of symptoms, they modestly decrease the intensity and duration of symptoms.

1.Mechanism of action: Influenza viruses employ a specific neuraminidase that is inserted into the host cell membrane for the purpose of releasing newly formed virions. This enzyme is essential for the virus life cycle. *Oseltamivir*, *zanamivir*, and *peramivir* selectively inhibit neuraminidase, thereby preventing the release of new virions and their spread from cell to cell.

2.Pharmacokinetics: *Oseltamivir* is an orally active prodrug that is rapidly hydrolyzed by the liver to its active form. *Zanamivir* is not active orally and is administered via inhalation. *Peramivir* is administered via intravenous (IV) infusion. All three drugs are eliminated unchanged in the urine (Figure 34.2).

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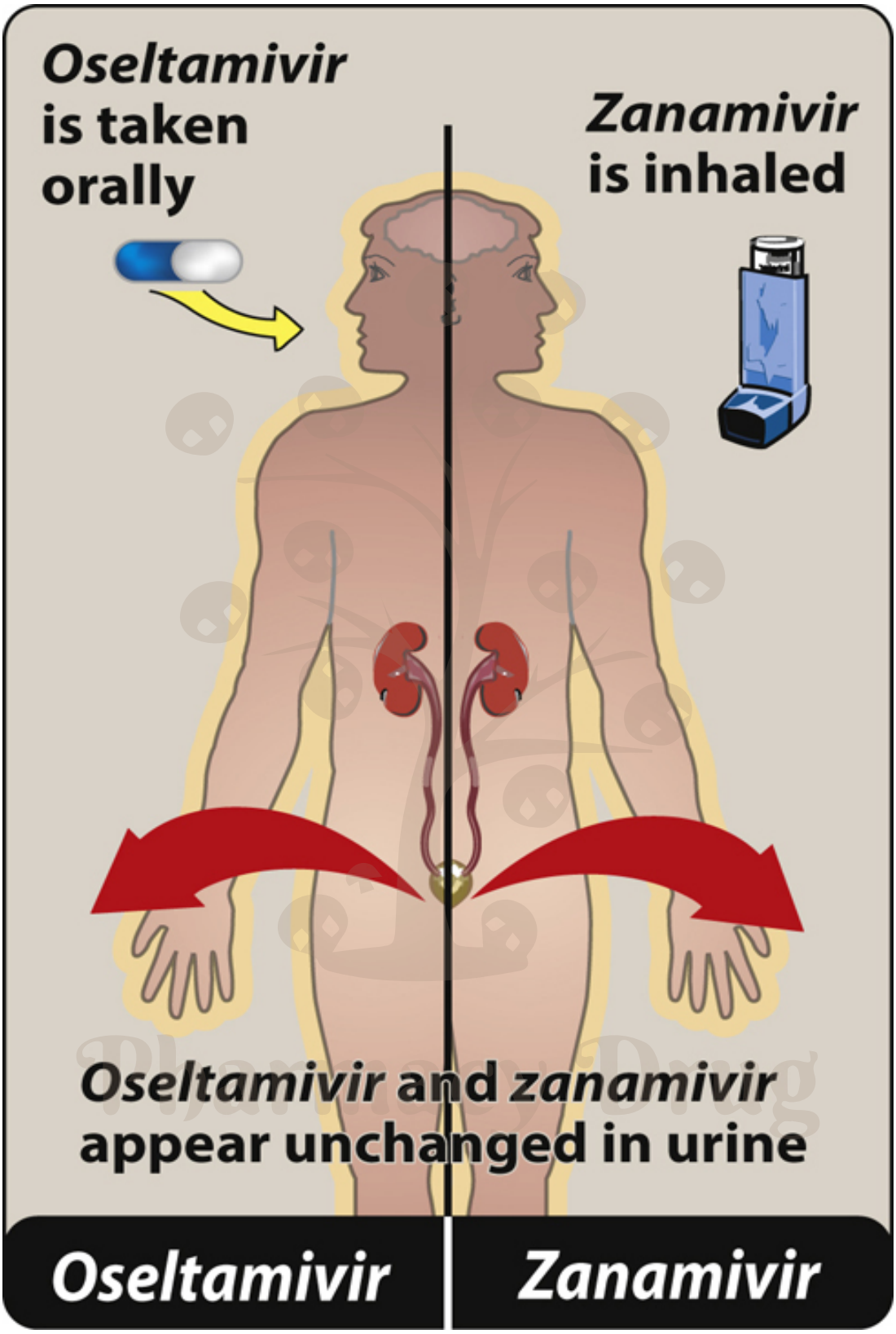

Figure 34.2 Administration and fate of *oseltamivir* and *zanamivir*.

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3.Adverse effects: The most common adverse effects of *oseltamivir* are gastrointestinal (GI) discomfort and nausea, which can be alleviated by taking the drug with food. Irritation of the respiratory tract occurs with *zanamivir.* It should be used with caution in individuals with asthma or chronic obstructive pulmonary disease because bronchospasm may occur. Diarrhea is a common adverse effect of *peramivir*.

4.Resistance: Mutations of the neuraminidase enzyme have been identified in adults treated with the neuraminidase inhibitors. These mutants, however, are often less infective and virulent than the wild type.

B. Endonucleotide inhibitor

Baloxavir marboxil [ba-LOX-A-veer mar-BOX-el] is an oral prodrug that is converted to *baloxavir*, an inhibitor of the endonuclease activity of a selective polymerase acidic protein in the influenza viral RNA polymerase. Inhibition of this influenza-specific enzyme prevents viral gene transcription and influenza virus replication. *Baloxavir marboxil* has demonstrated antiviral activity against influenza A and B viruses, including strains resistant to standard current antiviral agents. It is indicated within 48 hours of the onset of influenza symptoms, is administered orally as a single dose, and has a considerably long half-life (79.1 hours). Coadministration with dairy products, calcium-fortified beverages, polyvalent cation–containing laxatives or antacids, or oral supplements (for example, calcium, iron, magnesium, selenium, or zinc) should be avoided due to the possibility of chelation, decreasing *baloxavir* exposure. Diarrhea is a commonly reported adverse effect.

C. Adamantane antivirals

The therapeutic spectrum of the adamantane derivatives, *amantadine* [a-MAN-ta-deen] and *rimantadine* [ri-MAN-ta-deen], is limited to influenza A infections. Due to widespread resistance, the adamantanes are not recommended in the United States for the treatment or prophylaxis of influenza A.

D. Ribavirin

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Ribavirin [rye-ba-VYE-rin], a synthetic guanosine analog, is effective against a broad spectrum of RNA and DNA viruses. For example, *ribavirin* is used in the treatment of immunosuppressed infants and young children with severe RSV infections. *Ribavirin* is also effective in chronic hepatitis C infections when used in combination with other direct-acting antivirals (DAAs).

1.Mechanism of action: *Ribavirin* inhibits replication of RNA and DNA viruses. The drug is first phosphorylated to the 5′-phosphate derivatives. The major product *ribavirin* triphosphate exerts its antiviral action by inhibiting guanosine triphosphate formation, preventing viral messenger RNA (mRNA) capping, and blocking RNA-dependent RNA polymerase.

2.Pharmacokinetics: *Ribavirin* is effective orally and by inhalation. An aerosol is used in the treatment of RSV infection. Absorption is increased if the oral drug is taken with a fatty meal. The drug and its metabolites are eliminated in urine (Figure 34.3).

Pharmacy Drug

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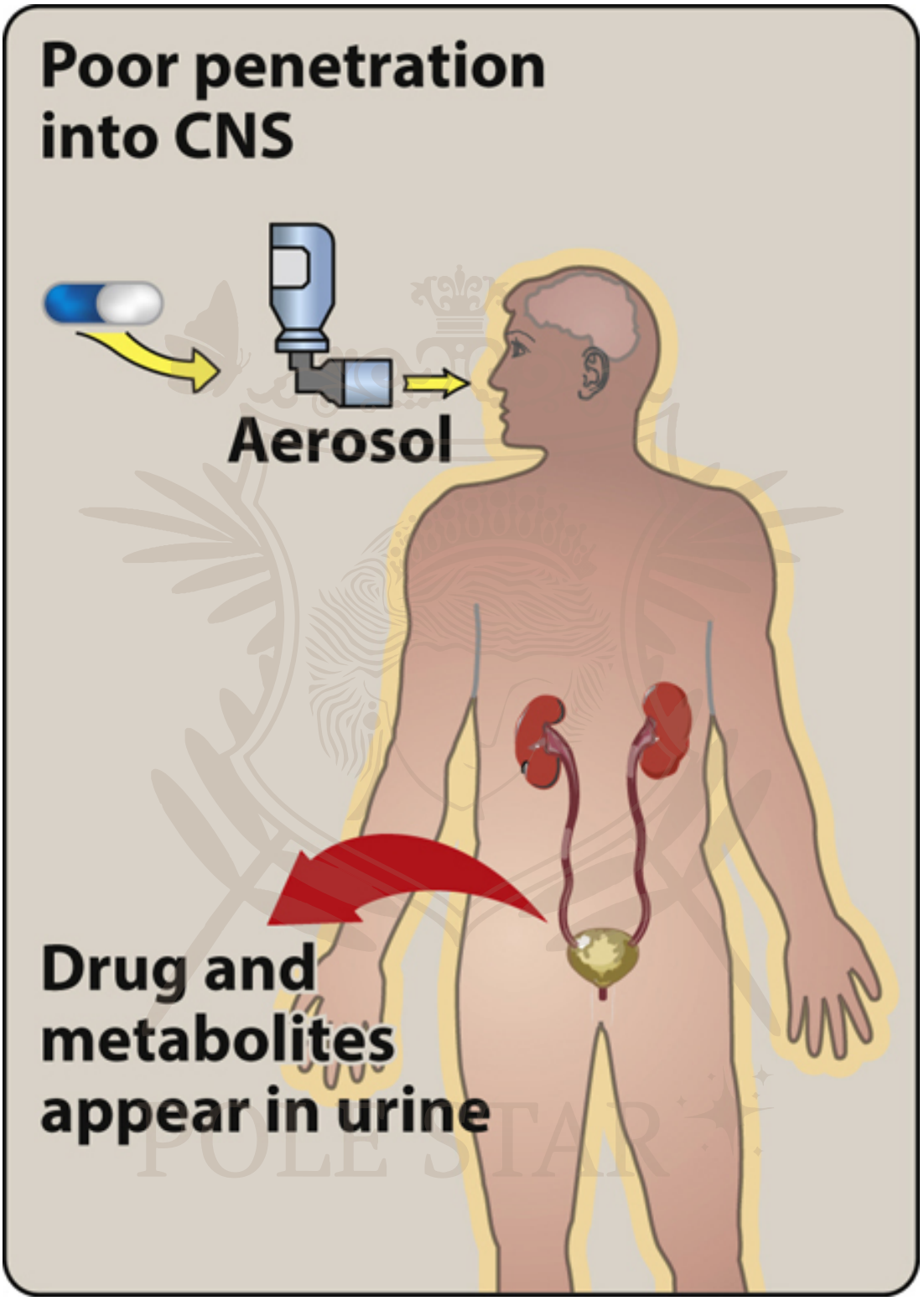

Figure 34.3 Administration and fate of *ribavirin*.CNS = central nervous system.

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3.Adverse effects: Adverse effects of *ribavirin* include dose-dependent transient anemia. Elevated bilirubin has also been reported. The aerosol may be safer, although respiratory function in infants can deteriorate quickly after initiation of aerosol treatment. Therefore, monitoring is essential. *Ribavirin* is contraindicated in pregnancy (Figure 34.4).

Figure 34.4 *Ribavirin* causes teratogenic effects.

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E. Remdesivir

Remdesivir [rem-DES-i-veer] is a prodrug of remdesivir triphosphate. This agent is an adenosine analog that inhibits SARS-CoV-2 RNA–dependent RNA polymerase, resulting in delayed chain termination and disruption of viral replication. *Remdesivir* is used for the treatment of hospitalized patients with COVID-19. The drug is administered by IV infusion. Renal and hepatic function should be monitored prior to and during therapy. *Remdesivir* is contraindicated in patients with an estimated glomerular filtration rate less than 30 mL/min/m^2. Adverse effects include diarrhea, increased hepatic enzymes, anemia, hyperglycemia, and hypersensitivity reactions. [Note: Several antiviral monoclonal antibodies for SARS-CoV-2, oral protease inhibitors (PIs) (for example, *nirmatrelvir/ritonavir*), and other oral antivirals (for example, *molnupiravir*) have been granted authorization as investigational drugs for the treatment of COVID-19. These agents are mainly used for patients with mild to moderate COVID-19 who are at risk of progressing to severe disease.]

III. TREATMENT OF HEPATIC VIRAL INFECTIONS

Each hepatitis virus currently identified (A, B, C, D, and E) has a pathogenesis, which specifically involves replication in and destruction of hepatocytes. Of this group, hepatitis B (a DNA virus) and hepatitis C (an RNA virus) are the most common causes of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (Figure 34.5) and are the only hepatic viral infections for which therapy is currently available. [Note: Hepatitis A is a commonly encountered infection caused by oral ingestion of the virus, but it is not a chronic disease.] Chronic hepatitis B may be treated with *peginterferon alfa-2a* [peg-in-ter-FEER-on AL-fa], which is injected subcutaneously once weekly. Oral therapy for chronic hepatitis B virus (HBV) includes *lamivudine* [la-MIV-yoo-deen], *adefovir* [a-DEF-o-veer], *entecavir* [en-TEK-a-vir], and *tenofovir* [ten-OF-oh-vir] (see Section VIII for *tenofovir*). The preferred treatment for chronic hepatitis C virus (HCV) is a combination of DAAs, the selection of which is based on the hepatitis C genotype. In certain cases, *ribavirin* is added to a DAA regimen to

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enhance virologic response. With the introduction of new DAAs, *pegylated interferon-α* is no longer commonly used in HCV, and it is not recommended in current guidelines due to inferior efficacy and poor tolerability.

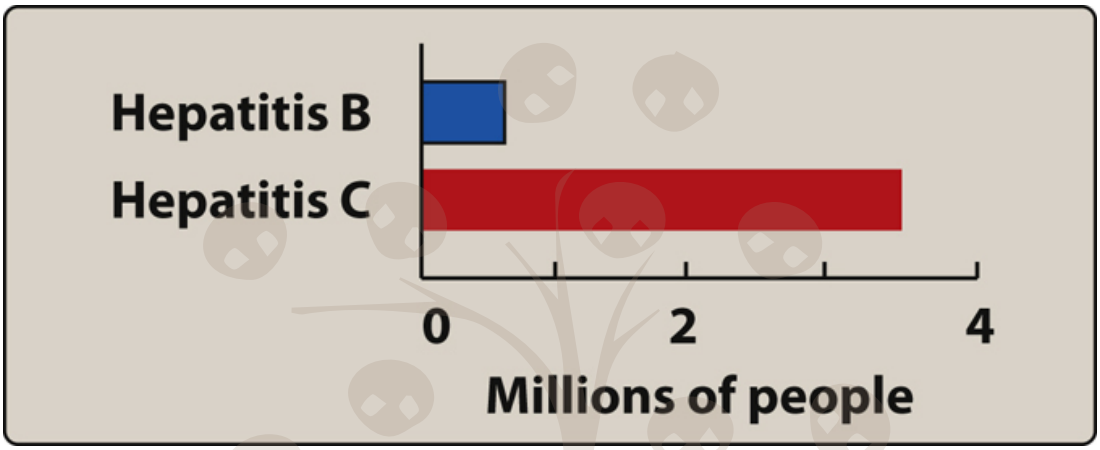

Figure 34.5 The prevalence of chronic hepatitis B and C in the United States.Data from Surveillance for Viral Hepatitis—United States 2015. Available at https://www.cdc.gov/hepatitis/statistics/2015surveillance/commentary.htm

IV. TREATMENT OF HEPATITIS B

A. Interferons

Interferons are a family of naturally occurring, inducible glycoproteins that interfere with the ability of viruses to infect cells. The interferons are synthesized by recombinant DNA technology. At least three types of interferons exist—α, β, and γ (Figure 34.6). In "pegylated" formulations, bis-monomethoxy polyethylene glycol has been covalently attached to *interferon-α* to increase the size of the molecule. The larger molecular size delays absorption from the injection site, lengthens the duration of action of the drug, and also decreases its clearance.

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Interferon-α	*Interferon-β*	*Interferon-γ*
Chronic hepatitis B and C	Relapsing-remitting multiple sclerosis	Chronic granulo-matous disease
Genital warts caused by papilloma-virus		
Hairy cell leukemia, Chronic myelogenous leukemia		
Kaposi sarcoma		

Figure 34.6 Some approved indications for *interferon*.

POLE STAR

1.Mechanism of action: The antiviral mechanism is incompletely understood. It appears to involve the induction of host cell enzymes that inhibit viral RNA translation, ultimately leading to the degradation of viral mRNA and tRNA.

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2.Therapeutic uses: *Peginterferon alfa-2a* is approved for the treatment of chronic HBV infection. It is also indicated for the treatment of HCV in combination with other agents, although the use is uncommon due to availability of more effective agents.

3.Adverse effects: These include flu-like symptoms, such as fever, chills, myalgias, arthralgias, and GI disturbances. Fatigue and mental depression are common. The principal dose-limiting toxicities are bone marrow suppression, severe fatigue and weight loss, neurotoxicity characterized by somnolence and behavioral disturbances, autoimmune disorders such as thyroiditis, and, rarely, cardiovascular problems such as heart failure.

B. Lamivudine

This cytosine analog is an inhibitor of both HBV and human immunodeficiency virus (HIV) reverse transcriptases (RTs). *Lamivudine* must be phosphorylated by host cellular enzymes to the triphosphate (active) form. This compound competitively inhibits HBV RNA–dependent DNA polymerase. As with many nucleotide analogs, the intracellular half-life of the triphosphate is many hours longer than its plasma half-life. The rate of HBV resistance is high following long-term therapy with *lamivudine* and, therefore, *lamivudine* is no longer recommended in current hepatitis B guidelines.

C. Adefovir

Adefovir is a nucleotide analog that is phosphorylated by cellular kinases to adefovir diphosphate, which is then incorporated into viral DNA. This leads to termination of chain elongation and prevents replication of HBV. Nephrotoxicity may occur with chronic use, and the drug should be used cautiously in patients with existing renal dysfunction. *Adefovir* is no longer recommended in current hepatitis B guidelines due to lower efficacy compared to other agents.

D. Entecavir

Entecavir is a guanosine nucleoside analog for the treatment of HBV infection. Following intracellular phosphorylation to the triphosphate, it competes with the natural substrate, deoxyguanosine triphosphate, for viral RT. *Entecavir* is effective against *lamivudine*-resistant strains of

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HBV and is dosed once daily. The drug is primarily excreted unchanged in the urine and dosage adjustments are needed in renal dysfunction. Concomitant use of drugs with renal toxicity should be avoided.

V. TREATMENT OF HEPATITIS C

HCV enters the hepatocyte following interaction with cellular entry factors. Once inside the cell, a viral genome is released from the nucleocapsid and an HCV polyprotein is translated using the internal ribosome entry site. The polyprotein is then cleaved by cellular and viral proteases to yield structural and nonstructural proteins. The core NS3 and NS5A proteins form the replication complex on lipid droplets and serve as a scaffold for RNA polymerase to replicate the viral genome, which is then packaged in envelope glycoproteins before noncytolytic secretion of mature virions. Several DAA agents targeting the NS3/NS4A protease, NS5B polymerase, and NS5A involved in HCV replication and assembly are available.

Combination therapy with DAAs is necessary to optimize HCV treatment response rates. Current combinations employ multiple DAAs that target different stages of the HCV life cycle simultaneously (Figure 34.7). With combination therapy, the agents are collectively able to suppress both wild-type and drug-resistant viral populations. Certain combinations may have different efficacy based on the genotype of HCV, and some are pangenotypic, meaning they have activity against all genotypes. It is anticipated that additional agents will be available in the near future. For a summary of current guidelines and regimens recommended in specific scenarios, see www.hcvguidelines.org.

POLE STAR

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GENERIC NAME(S)	BRAND NAME(S)	APPROVED HCV GENOTYPES
Elbasvir/grazoprevir	Zepatier	1, 4
Glecaprevir/pibrentasvir	Mavyret	1, 2, 3, 4, 5, 6
Sofosbuvir/ledipasvir	Harvoni	1, 4, 5, 6
Sofosbuvir/velpatasvir	Epclusa	1, 2, 3, 4, 5, 6
Sofosbuvir/velpatasvir/voxilaprevir	Vosevi	1, 2, 3, 4, 5, 6

Figure 34.7 Combinations of direct-acting antiviral agents for treatment of hepatitis C virus.HCV = hepatitis C virus.

A. NS3/NS4A protease inhibitors

The viral NS3/NS4A serine protease is crucial for processing the single polyprotein encoded by HCV RNA into individually active-proteins, NS4A, NS4B, NS5A, and NS5B. Without these serine proteins, RNA replication does not occur and the HCV life cycle is effectively disrupted. *Grazoprevir* [graz-OH-pre-vir], *voxilaprevir* [VOX-i-LA-pre-vir], and *glecaprevir* [glec-A-pre-vir] are DAAs that inhibit the NS3/NS4A serine protease as their primary mechanism of action. [Note: HCV PIs often have the ending "-previr."] These drugs have a lower barrier to resistance than other agents, such as *sofosbuvir.* The use of HCV PIs presents significant potential for drug–drug interactions due to their metabolism by CYP3A enzymes. Decompensated cirrhosis is a contraindication for use due to increased drug exposure and risk of liver decompensation. Adverse effects of NS3/NS4A PIs include rash, pruritus, nausea, fatigue, and anemia.

B. NS5B polymerase inhibitors

NS5B is the sole RNA polymerase responsible for HCV replication and is processed with other HCV proteins into an individual polypeptide by the viral NS3/NS4A serine protease. *Sofosbuvir* [soe-FOS-bue-vir] is currently the only NS5B nucleotide polymerase inhibitor for the treatment of HCV infection. [Note: NS5B inhibitors often end in "-buvir."] NS5B polymerase inhibitors are well tolerated with few adverse effects.

C. NS5A replication complex inhibitors

@Pharmacy_Z

NS5A is a viral protein that is essential for HCV RNA replication and assembly. Its role in replication appears to be the formation of a membranous web along with viral protein NS4B, and this web provides a platform for replication. The currently available NS5A inhibitors include *ledipasvir* [le-DIP-as-vir], *elbasvir* [ELB-as-vir], *pibrentasvir* [pi-BRENT-as-vir], and *velpatasvir* [vel-PAT-as-vir]. [Note: NS5A inhibitors often end in "-asvir."] These agents are all coformulated with other DAAs (see Figure 34.7). NS5A inhibitors have a number of clinically significant drug interactions due to their metabolism by hepatic CYP450 isoenzymes and inhibition of P-glycoprotein (P-gp). Absorption of *ledipasvir* is reduced when gastric pH is increased. Patients receiving proton pump inhibitors should either stop these agents during HCV therapy with *ledipasvir* or take the proton pump inhibitor with *ledipasvir*-containing regimens under fasted conditions to ensure that gastric pH is at its lowest point at the time of drug administration.

D. Ribavirin

Ribavirin is approved for the treatment of chronic HCV when used in combination with standard or *pegylated interferon* or with DAAs. *Ribavirin*, a guanosine analog, improves viral clearance, decreases relapse rates, and improves rates of sustained virologic response when used in combination with other agents. The addition of *ribavirin* to DAA-based regimens is based on HCV genotype/subtype, cirrhosis status, mutational status, and treatment history. Despite its use in patients with HCV for more than 20 years, the precise mechanism(s) by which *ribavirin* improves outcomes is unknown. *Ribavirin* remains an important component of HCV therapy, even in the age of DAA therapy. Whether use of *ribavirin* will be necessary with future DAAs is not known. The dose of *ribavirin* is always weight based, and it is administered in two daily divided doses with food.

VI. TREATMENT OF HERPES VIRUS INFECTIONS

Herpes viruses are associated with a broad spectrum of diseases, for example, cold sores, viral encephalitis, and genital infections. The drugs

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that are effective against these viruses exert their actions during the acute phase of viral infections and are without effect during the latent phase.

A. Acyclovir

Acyclovir [ay-SYE-kloe-veer] is the prototypic antiherpetic therapeutic agent. Herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus (VZV), and some Epstein–Barr virus–mediated infections are sensitive to *acyclovir.* It is the treatment of choice in HSV encephalitis. The most common use of *acyclovir* is in therapy for genital herpes infections. It is also given prophylactically to seropositive patients before bone marrow transplant and post-heart transplant to protect such individuals from herpetic infections.

1.Mechanism of action: *Acyclovir*, a guanosine analog, is monophosphorylated in the cell by the herpesvirus-encoded enzyme thymidine kinase (Figure 34.8). Therefore, virus-infected cells are most susceptible. The monophosphate analog is converted to the di- and triphosphate forms by the host cell kinases. Acyclovir triphosphate competes with deoxyguanosine triphosphate as a substrate for viral DNA polymerase and is itself incorporated into the viral DNA, causing premature DNA chain termination.

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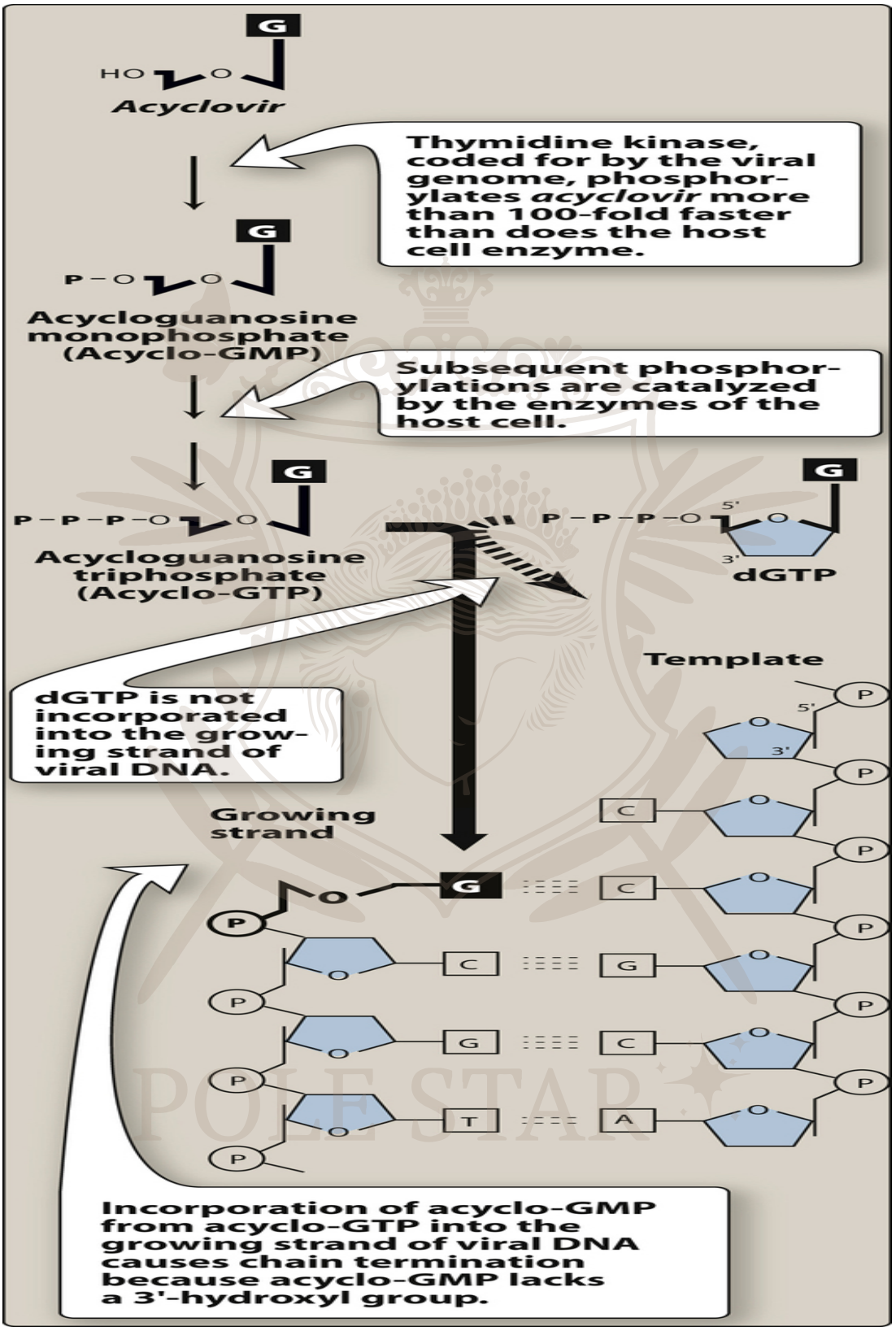
G
HO
O
Acyclovir
Thymidine kinase, coded for by the viral genome, phosphorylates acyclovir more than 100-fold faster than does the host cell enzyme.
G
P – O
O
Acycloguanosine monophosphate (Acyclo-GMP)
Subsequent phosphorylations are catalyzed by the enzymes of the host cell.
G
P – P – P – O
O
Acycloguanosine triphosphate (Acyclo-GTP)
G
P – P – P – O
5'
O
3'
dGTP
dGTP is not incorporated into the growing strand of viral DNA.
Template
Growing strand
P
O
5'
3'
C
G
T
A
Incorporation of acyclo-GMP from acyclo-GTP into the growing strand of viral DNA causes chain termination because acyclo-GMP lacks a 3'-hydroxyl group.

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Figure 34.8 Incorporation of *acyclovir* into replicating viral DNA, causing chain termination.dGTP = deoxyguanosine triphosphate.

2.Pharmacokinetics: *Acyclovir* is administered by IV, oral, or topical routes. [Note: The efficacy of topical applications is questionable.] The drug distributes well throughout the body, including the cerebrospinal fluid (CSF). *Acyclovir* is partially metabolized to an inactive product. Excretion into the urine occurs both by glomerular filtration and tubular secretion (Figure 34.9). *Acyclovir* accumulates in patients with renal failure. The valyl ester, *valacyclovir* [val-a-SYE-kloe-veer], has greater oral bioavailability than *acyclovir.* This ester is rapidly hydrolyzed to *acyclovir* and achieves levels of the latter comparable to those of *acyclovir* following IV administration.

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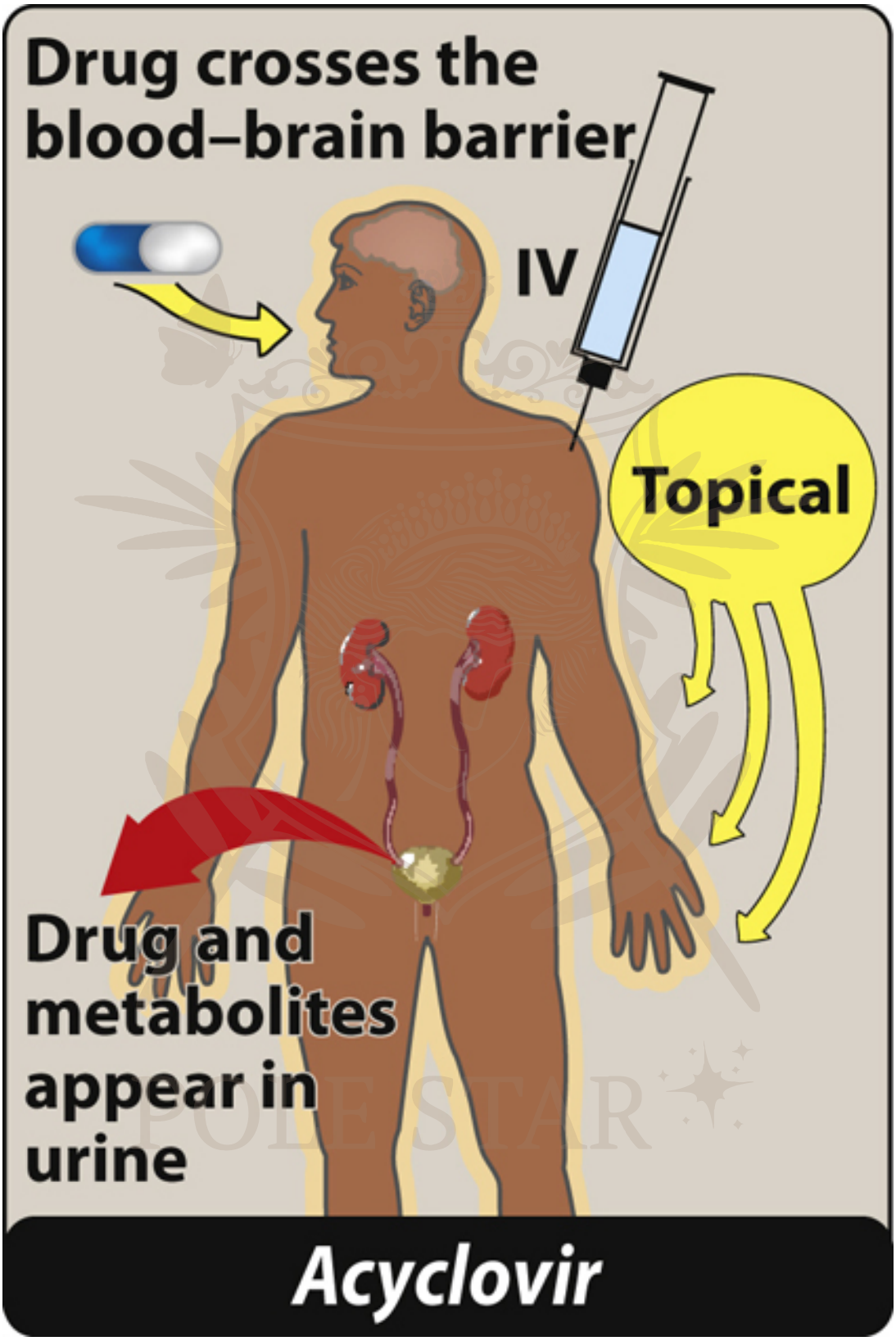

Figure 34.9 Administration and fate of *acyclovir*.IV = intravenous.

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3.Adverse effects: Adverse effects of *acyclovir* treatment depend on the route of administration. For example, local irritation may occur from topical application; headache, diarrhea, nausea, and vomiting may result after oral administration. Transient renal dysfunction may occur at high doses or in a dehydrated patient receiving the drug intravenously.

4.Resistance: Altered or deficient thymidine kinase and DNA polymerases have been found in some resistant viral strains and are most commonly isolated from immunocompromised patients. Cross-resistance to the other agents in this family occurs.

B. Cidofovir

Cidofovir [si-DOE-foe-veer] is indicated for the treatment of cytomegalovirus (CMV) retinitis in patients with AIDS. [Note: CMV is a member of the herpesvirus family.] *Cidofovir* is a nucleotide analog of cytosine, the phosphorylation of which is not dependent on viral or cellular enzymes. It inhibits viral DNA synthesis. Slow elimination of the active intracellular metabolite permits prolonged dosage intervals and eliminates the permanent venous access needed for *ganciclovir* therapy. *Cidofovir* is administered intravenously. *Cidofovir* produces significant renal toxicity (Figure 34.10), and it is contraindicated in patients with preexisting renal impairment and in those taking nephrotoxic drugs. Neutropenia and metabolic acidosis also occur. Oral *probenecid* and IV normal saline are coadministered with *cidofovir* to reduce the risk of nephrotoxicity. Since the introduction of highly active antiretroviral therapy (ART), the prevalence of CMV infections in immunocompromised hosts has markedly declined, as has the importance of *cidofovir* in the treatment of these patients.

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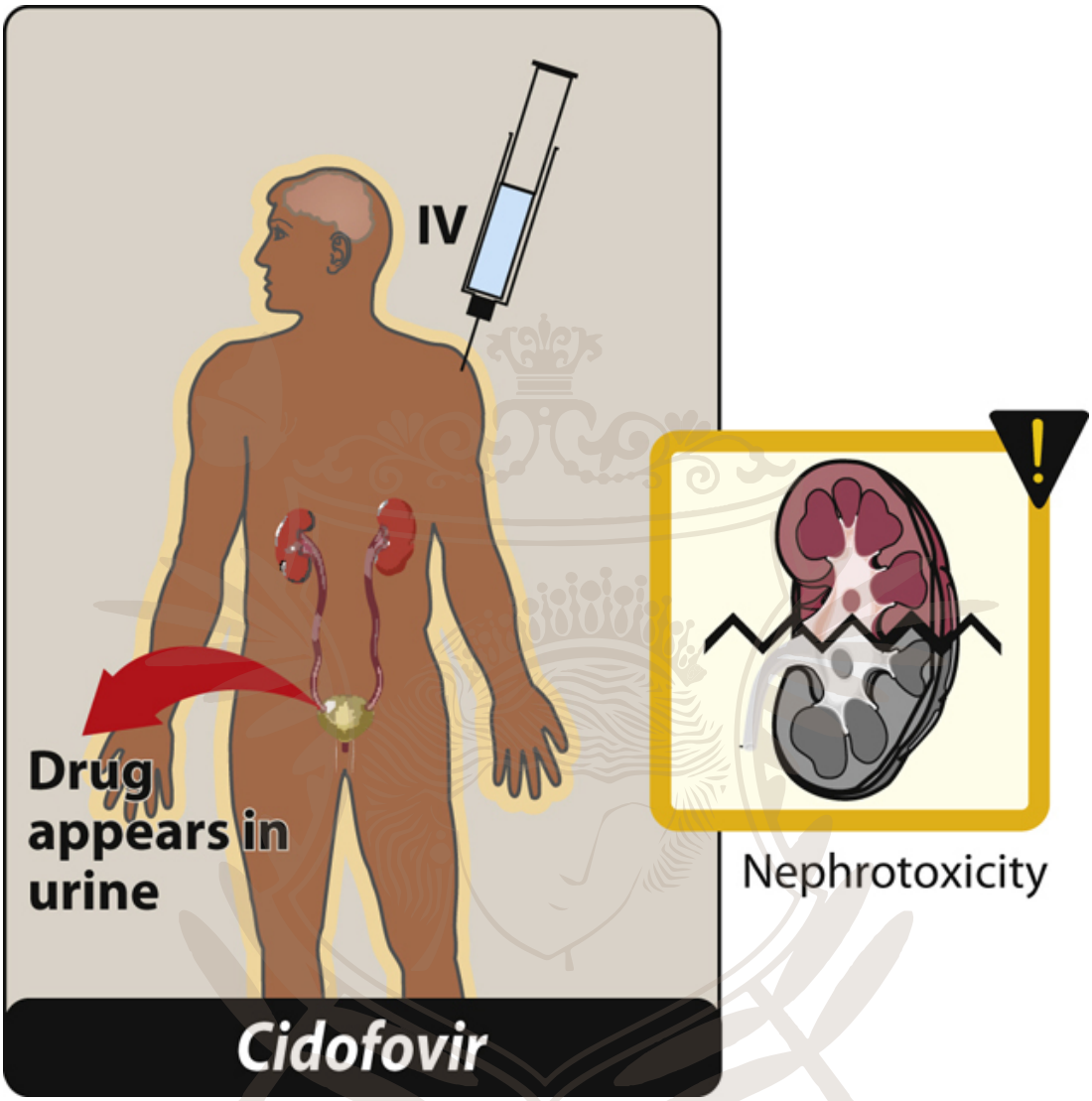

Figure 34.10 Administration, fate, and toxicity of *cidofovir*.IV = intravenous.

C. Foscarnet

Unlike most antiviral agents, *foscarnet* [fos-KAR-net] is not a purine or pyrimidine analog. Instead, it is a pyrophosphate derivative and does not require activation by viral (or cellular) kinases. *Foscarnet* is approved for CMV retinitis in immunocompromised hosts and for *acyclovir*-resistant HSV infections. *Foscarnet* works by reversibly inhibiting viral DNA and RNA polymerases, thereby interfering with viral DNA and RNA synthesis. Mutation of the polymerase structure is responsible for resistant viruses. *Foscarnet* is poorly absorbed orally

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and must be injected intravenously. It must also be given frequently to avoid relapse when plasma levels fall. It is dispersed throughout the body, and greater than 10% enters the bone matrix, from which it slowly disperses. The parent drug is eliminated by glomerular filtration and tubular secretion (Figure 34.11). Adverse effects include nephrotoxicity, anemia, nausea, and fever. Due to chelation with divalent cations, hypocalcemia and hypomagnesemia are also seen. In addition, hypokalemia, hypo- and hyperphosphatemia, seizures, and arrhythmias have been reported.

Pharmacy Drug

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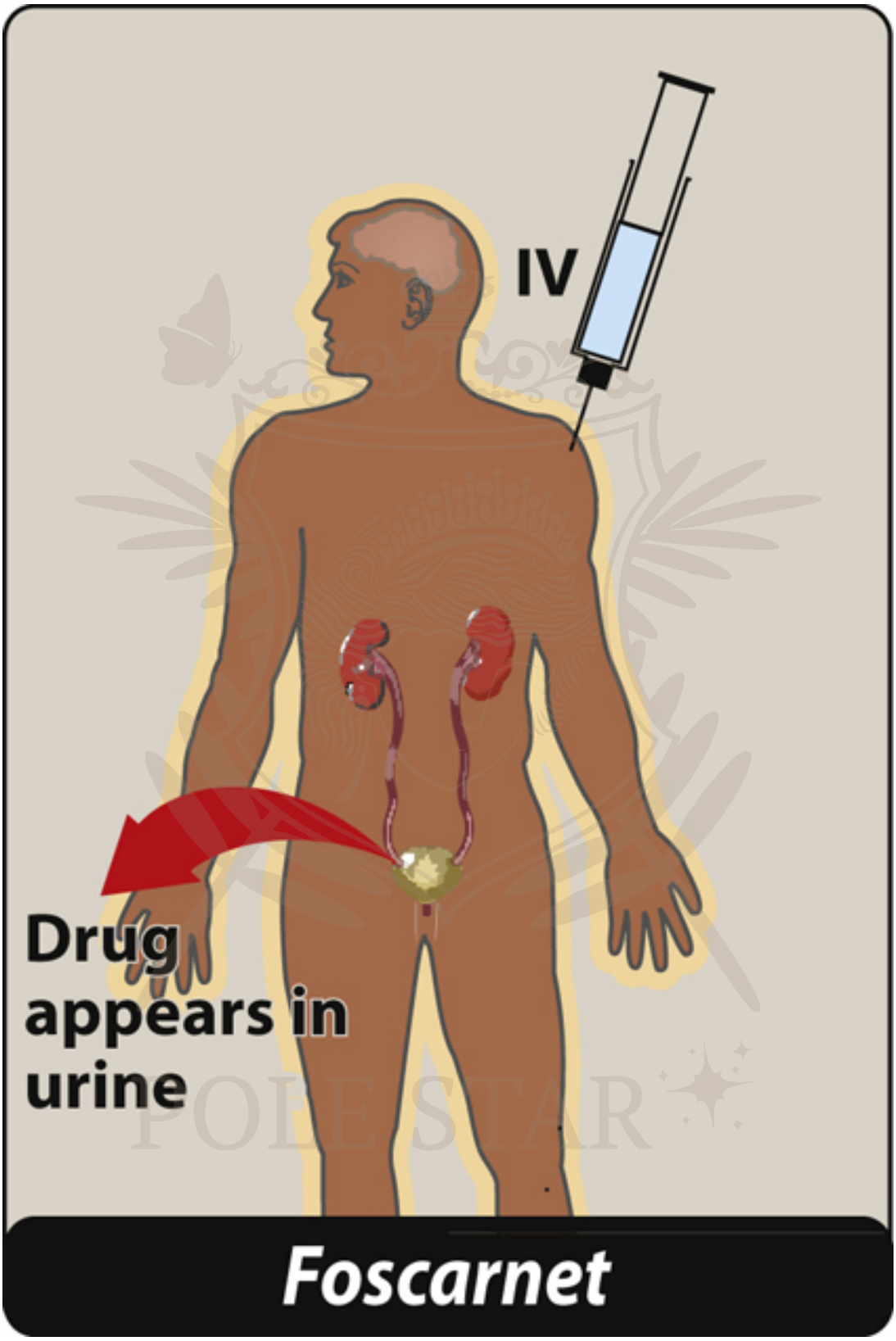

Figure 34.11 Administration and fate of *foscarnet*.

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D. Ganciclovir

Ganciclovir [gan-SYE-kloe-veer] is an analog of *acyclovir* that has greater activity against CMV. It is used for the treatment of CMV retinitis in immunocompromised patients and for CMV prophylaxis in transplant patients. Like *acyclovir*, *ganciclovir* is activated through conversion to the nucleoside triphosphate by viral and cellular enzymes. The nucleotide inhibits viral DNA polymerase and can be incorporated into the DNA resulting in chain termination. *Ganciclovir* is administered IV and distributes throughout the body, including the CSF. Excretion into the urine occurs through glomerular filtration and tubular secretion (Figure 34.12). Like *acyclovir*, *ganciclovir* accumulates in patients with renal failure. *Valganciclovir* [val-gan-SYE-kloe-veer], an oral drug, is the valyl ester of *ganciclovir.* Like *valacyclovir*, *valganciclovir* has high oral bioavailability because rapid hydrolysis in the intestine and liver after oral administration leads to high levels of *ganciclovir.* Adverse effects include severe, dose-dependent neutropenia. *Ganciclovir* is carcinogenic as well as teratogenic and carries a boxed warning for use in pregnancy. Resistant CMV strains that have lower levels of ganciclovir triphosphate have been detected.

Pharmacy Drug

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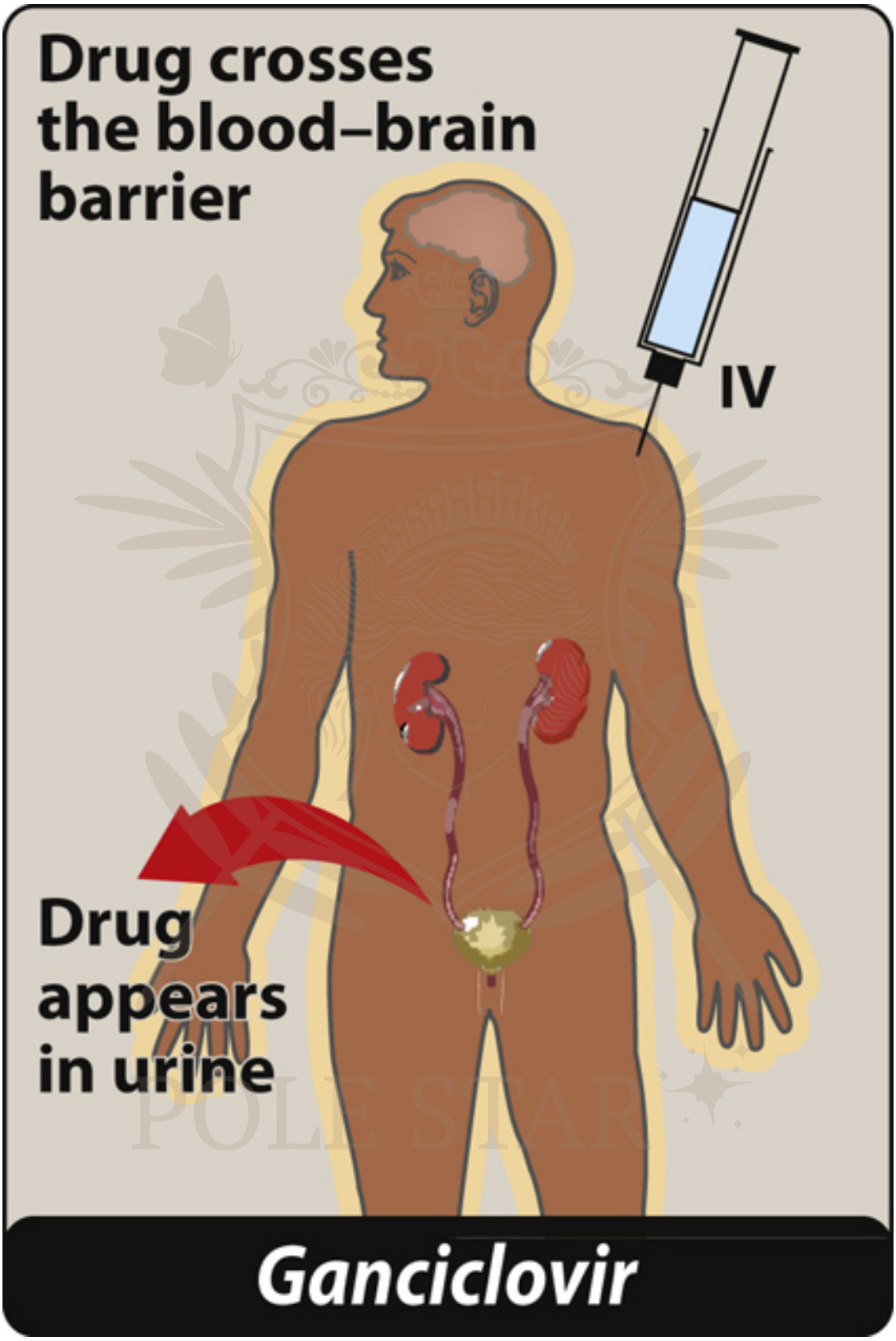

Figure 34.12 Administration and fate of *ganciclovir*.

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E. Penciclovir and famciclovir

Penciclovir [pen-SYE-kloe-veer] is an acyclic guanosine nucleoside derivative that is active against HSV-1, HSV-2, and VZV. *Penciclovir* is administered topically (Figure 34.13). It is monophosphorylated by viral thymidine kinase, and cellular enzymes form the nucleoside triphosphate, which inhibits HSV DNA polymerase. Penciclovir triphosphate has an intracellular half-life much longer than acyclovir triphosphate. *Penciclovir* is negligibly absorbed upon topical application and is well tolerated. *Famciclovir* [fam-SYE-kloe-veer], another acyclic analog of 2′-deoxyguanosine, is a prodrug that is metabolized to the active *penciclovir.* The antiviral spectrum is similar to that of *ganciclovir*, and it is approved for treatment of acute herpes zoster, genital HSV infection, and recurrent herpes labialis. The drug is effective orally (Figure 34.13). Adverse effects include headache and nausea.

Pharmacy Drug

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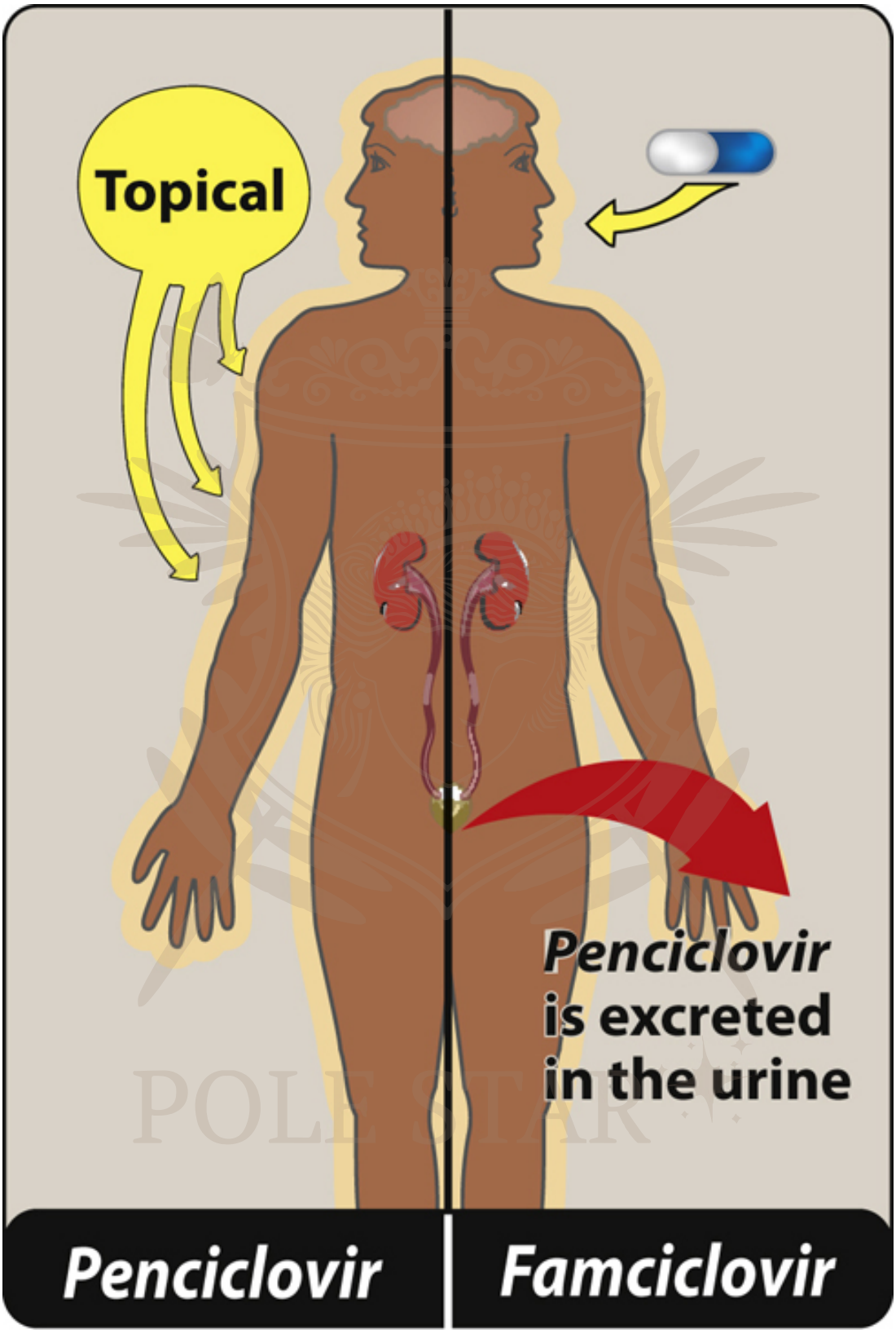

Figure 34.13 Administration and fate of *penciclovir* and *famciclovir*.

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F. Trifluridine

Trifluridine [trye-FLURE-i-deen] is a fluorinated pyrimidine nucleoside analog that is structurally similar to thymidine. Once converted to the triphosphate, the agent is believed to inhibit the incorporation of thymidine triphosphate into viral DNA and, to a lesser extent, lead to the synthesis of defective DNA that renders the virus unable to replicate. *Trifluridine* is active against HSV-1, HSV-2, and vaccinia virus. It is indicated for treatment of HSV keratoconjunctivitis and recurrent epithelial keratitis. Because the triphosphate form of *trifluridine* can also incorporate to some degree into cellular DNA, the drug is too toxic for systemic use. Therefore, the use of *trifluridine* is restricted to a topical ophthalmic preparation. A short half-life necessitates that the drug be applied frequently. Adverse effects include a transient irritation of the eye and palpebral (eyelid) edema.

Figure 34.14 summarizes selected antiviral agents.

Pharmacy Drug

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Antiviral drug	Mechanism of action	Viruses or diseases affected
Acyclovir	Metabolized to acyclovir triphosphate, which inhibits viral DNA polymerase	Herpes simplex, varicella-zoster, cytomegalovirus
Adefovir	Inhibition of viral DNA polymerase and reverse transcriptase	Hepatitis B (chronic cases)
Amantadine	Blockage of the M2 protein ion channel and its ability to modulate intracellular pH	Influenza A
Baloxavir marboxil	Inhibits endonuclease activity of a selective polymerase acidic protein required for viral gene transcription, resulting in inhibition of viral replication	Influenza A and B
Cidofovir	Inhibition of viral DNA polymerase	Cytomegalovirus; indicated only for virus-induced retinitis
Entecavir	Inhibition of viral polymerase and reverse transcriptase	Hepatitis B
Famciclovir	Same as *penciclovir*	Herpes simplex, varicella-zoster
Foscarnet	Inhibition of viral DNA polymerase and reverse transcriptase at the pyrophosphate-binding site	Cytomegalovirus, *acyclovir*-resistant herpes simplex, *acyclovir*-resistant varicella-zoster
Ganciclovir	Inhibits viral DNA polymerase	Cytomegalovirus
Interferon-α	Induction of cellular enzymes that interfere with viral protein synthesis	Hepatitis B and C, human herpesvirus 8, papilloma virus, Kaposi sarcoma, hairy cell leukemia, chronic myelogenous leukemia
Lamivudine	Inhibition of viral DNA polymerase and reverse transcriptase	Hepatitis B (chronic cases), human immunodeficiency virus type 1
Oseltamivir	Inhibition of viral neuraminidase	Influenza A and B
Penciclovir	Metabolized to penciclovir triphosphate, which inhibits viral DNA polymerase	Herpes simplex
Peramivir	Inhibition of viral neuraminidase	Influenza A and B
Remdesivir	Inhibition of SARS-CoV-2 RNA–dependent RNA polymerase	SARS-CoV-2 (COVID-19)
Ribavirin	Interference with viral messenger RNA	Lassa fever, hantavirus (hemorrhagic fever renal syndrome), hepatitis C (in combination with direct-acting antiviral agents), RSV in children and infants
Rimantadine	Blockage of the M2 protein ion channel and its ability to modulate intracellular pH	Influenza A
Trifluridine	Inhibits thymidylate synthetase	Herpes keratoconjunctivitis and keratitis
Valacyclovir	Same as *acyclovir*	Herpes simplex, varicella-zoster, cytomegalovirus
Valganciclovir	Same as *ganciclovir*	Cytomegalovirus
Zanamivir	Inhibition of viral neuraminidase	Influenza A and B

Figure 34.14 Summary of selected antiviral agents.RSV = respiratory syncytial virus.Data from H. H.Balfour . Antiviral drugs. *N. Engl. J. Med*. 340: 1255 (1999).

POLE STAR

VII. TREATMENT OF HIV INFECTION

Prior to approval of *zidovudine* [zye-DOE-vyoo-deen] in 1987, treatment of HIV infections focused on decreasing the occurrence of opportunistic

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infections that caused a high degree of morbidity and mortality in patients with AIDS. Today, the viral life cycle is understood (Figure 34.15), and a combination of drugs is used to suppress replication of HIV and restore the number of CD4 cells and immunocompetence to the host. This multidrug regimen is commonly referred to as ART (Figure 34.16). There are five classes of antiretroviral drugs, each of which targets one of the four viral processes. These classes of drugs are nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), PIs, entry inhibitors, and the integrase inhibitors. There are also two pharmacokinetic enhancers, also known as “boosters,” which lack anti-HIV activity themselves, but rather serve to increase drug levels of concomitantly administered antiretroviral agents and allow for less frequent dosing and less variation in drug levels. Initial therapy for HIV consists of a combination of two NRTIs with an integrase inhibitor, an NNRTI, or a boosted PI. In some instances, one NRTI with an integrase inhibitor may be utilized. Selection of the appropriate combination is based on (1) avoidance of the use of two agents of the same nucleoside analog; (2) avoidance of overlapping toxicities and genotypic and phenotypic characteristics of the virus; (3) patient factors, such as disease symptoms and concurrent illnesses; (4) impact of drug interactions; and (5) ease of adherence to the regimen. The goals of therapy are to maximally and durably suppress HIV RNA replication, to restore and preserve immunologic function, to reduce HIV-related morbidity and mortality, to improve quality of life, and to prevent HIV transmission to others.

Pharmacy Drug

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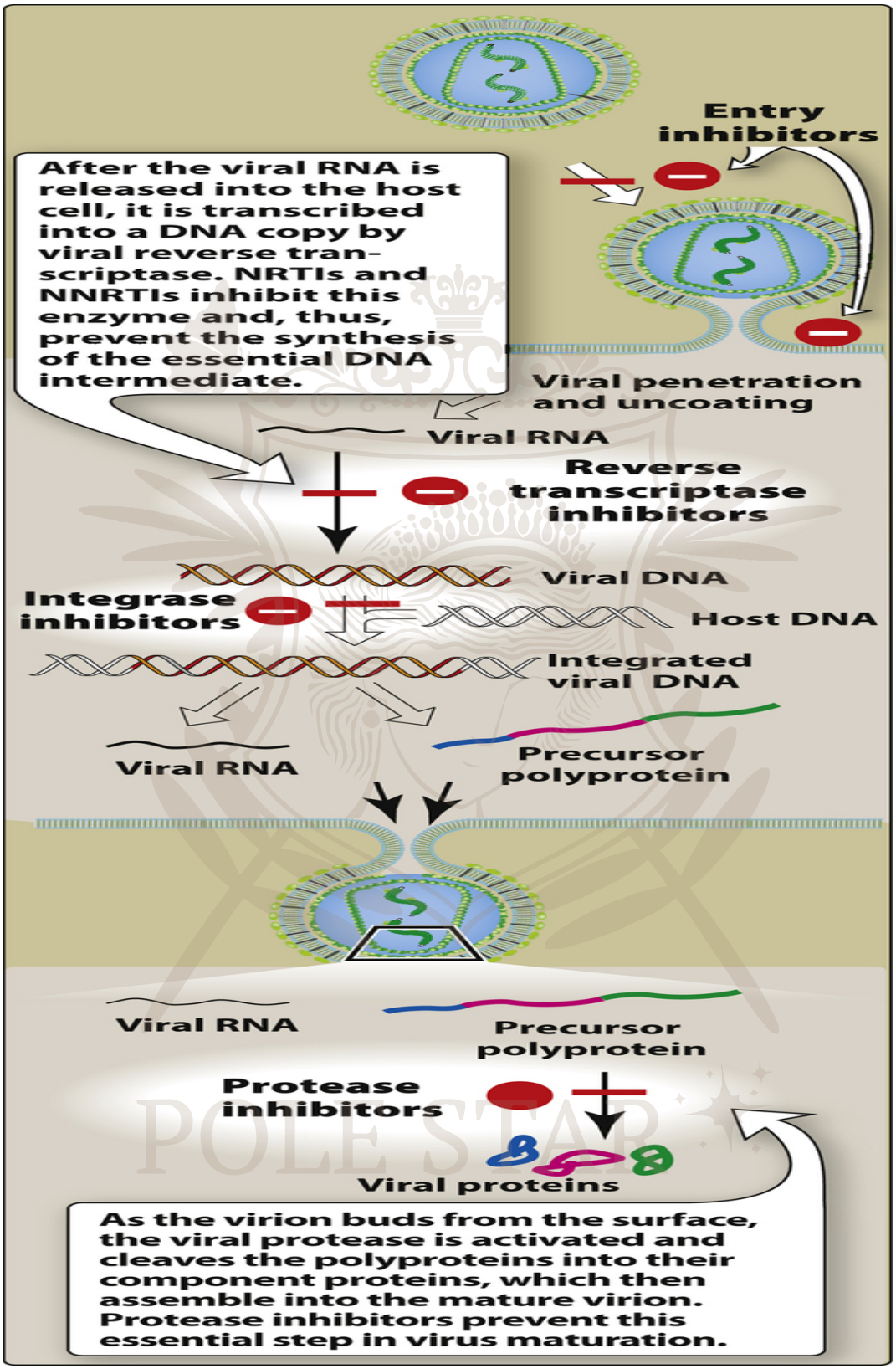
Entry inhibitors
After the viral RNA is released into the host cell, it is transcribed into a DNA copy by viral reverse transcriptase. NRTIs and NNRTIs inhibit this enzyme and, thus, prevent the synthesis of the essential DNA intermediate.
Viral penetration and uncoating
Viral RNA
Reverse transcriptase inhibitors
Viral DNA
Integrase inhibitors
Host DNA
Integrated viral DNA
Viral RNA
Precursor polyprotein
Viral RNA
Precursor polyprotein
Protease inhibitors
Viral proteins
As the virion buds from the surface, the viral protease is activated and cleaves the polyproteins into their component proteins, which then assemble into the mature virion. Protease inhibitors prevent this essential step in virus maturation.

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Figure 34.15 Drugs used to prevent human immunodeficiency virus from replicating.NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside and nucleotide reverse transcriptase inhibitor.

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A Currently available drugs

Nucleoside/-tide reverse transcriptase inhibitors:

- *Abacavir*
- *Emtricitabine*
- *Lamivudine*
- *Tenofovir*
- *Zidovudine*

Nonnucleoside reverse transcriptase inhibitors:

- *Doravirine*
- *Efavirenz*
- *Etravirine*
- *Nevirapine*
- *Rilpivirine*

Protease inhibitors:

- *Atazanavir*
- *Darunavir*
- *Fosamprenavir*
- *Lopinavir/ritonavir*
- *Nelfinavir*
- *Saquinavir*
- *Tipranavir*

Entry inhibitors:

- *Enfuvirtide*
- *Fostemsavir*
- *Ibalizumab*
- *Maraviroc*

Integrase inhibitors:

- *Bictegravir*
- *Cabotegravir*
- *Dolutegravir*
- *Elvitegravir*
- *Raltegravir*

B Combination therapy

Two nucleoside/-tide reverse transcriptase inhibitors

plus

One protease inhibitor + *ritonavir* or *cobicistat*

or

A nonnucleoside reverse transcriptase inhibitor

or

An integrase inhibitor

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Figure 34.16 Antiretroviral therapy for treatment of human immunodeficiency virus.

VIII. NRTIS USED TO TREAT HIV INFECTION

A. Overview of NRTIs

NRTIs were the first agents available to treat HIV infection, and currently, the use of two NRTIs is a mainstay of most initial antiretroviral regimens. Available NRTIs include *zidovudine*, *lamivudine*, *emtricitabine* [em-trye-SYE-ta-been], *tenofovir*, *didanosine* [dye-DAN-oh-seen], and *abacavir* [a-BAK-a-veer]. The most commonly used NRTIs are *tenofovir*, *abacavir*, *emtricitabine*, and *lamivudine*, and these NRTIs are recommended parts of initial regimens for most patients with HIV. *Tenofovir disoproxil fumarate* (TDF) or *tenofovir alafenamide* (TAF) in combination with *emtricitabine* can also be used for preexposure prophylaxis in individuals at high risk for HIV acquisition.

1.Mechanism of action: These agents are inhibitors of HIV RT. NRTIs are analogs of native ribosides (nucleosides or nucleotides containing ribose), which all lack a 3′-hydroxyl group. Once they enter cells, they are phosphorylated by cellular enzymes to the corresponding triphosphate analog, which is preferentially incorporated into the viral DNA by RT. Because the 3′-hydroxyl group is not present, a 3′,5′-phosphodiester bond between an incoming nucleoside triphosphate and the growing DNA chain cannot be formed, and DNA chain elongation is terminated. Affinities of the drugs for many host cell DNA polymerases are lower than they are for HIV RT, although mitochondrial DNA polymerase γ appears to be susceptible at therapeutic concentrations.

2.Pharmacokinetics: All of the NRTIs are administered orally. [Note: *Zidovudine* is also available as an IV formulation.] *Tenofovir* is available in two different salt forms as TDF and TAF, both

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prodrugs of *tenofovir.* The *tenofovir* prodrug is converted by lymphoid cellular enzymes to tenofovir diphosphate, which is the active form of the drug and an inhibitor of HIV RT. TAF achieves improved anti-HIV activity at lower doses than TDF, resulting in a five- to sevenfold increase in intracellular diphosphate in the lymphoid cell and in lower circulating plasma *tenofovir* levels. Because of this, TAF has fewer adverse effects (renal insufficiency and loss of bone mineral density) than TDF. The NRTIs are primarily renally excreted, and all require dosage adjustment in renal insufficiency except *abacavir*, which is metabolized by alcohol dehydrogenase and glucuronyl transferase.

3.Adverse effects: Many toxicities of the NRTIs are believed to be due to inhibition of the mitochondrial DNA polymerase in certain tissues. As a general rule, the dideoxynucleosides, such as *didanosine*, have a greater affinity for the mitochondrial DNA polymerase, leading to toxicities such as peripheral neuropathy, pancreatitis, and lipoatrophy. Because of these mitochondrial toxicities, *didanosine* is rarely used in current antiretroviral regimens. When more than one NRTI is given, care is taken to avoid overlapping toxicities. All NRTIs have been associated with potentially fatal liver toxicity characterized by lactic acidosis and hepatomegaly with steatosis. *Abacavir* is associated with a hypersensitivity reaction, which affects approximately 5% of patients and is usually characterized by drug fever, plus a rash, GI symptoms, malaise, or respiratory distress (Figure 34.17). Sensitized individuals should *never* be rechallenged with *abacavir* because of rapidly appearing, severe reactions that may lead to death. A genetic test (HLA-B*5701) is available to screen patients for the potential of this reaction. Figure 34.18 shows some adverse reactions commonly seen with nucleoside analogs.

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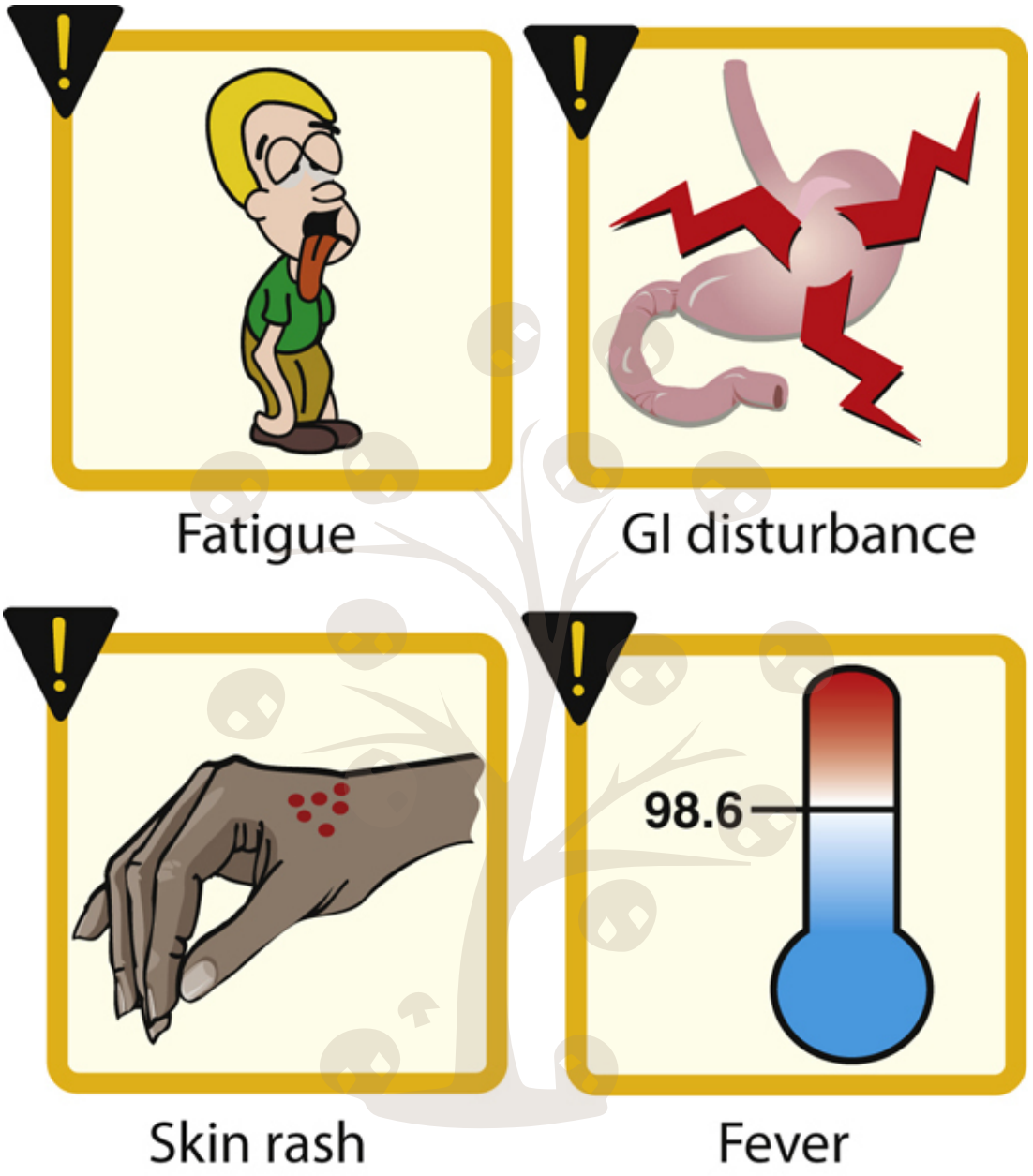

Figure 34.17 Hypersensitivity reactions to *abacavir*.GI = gastrointestinal.

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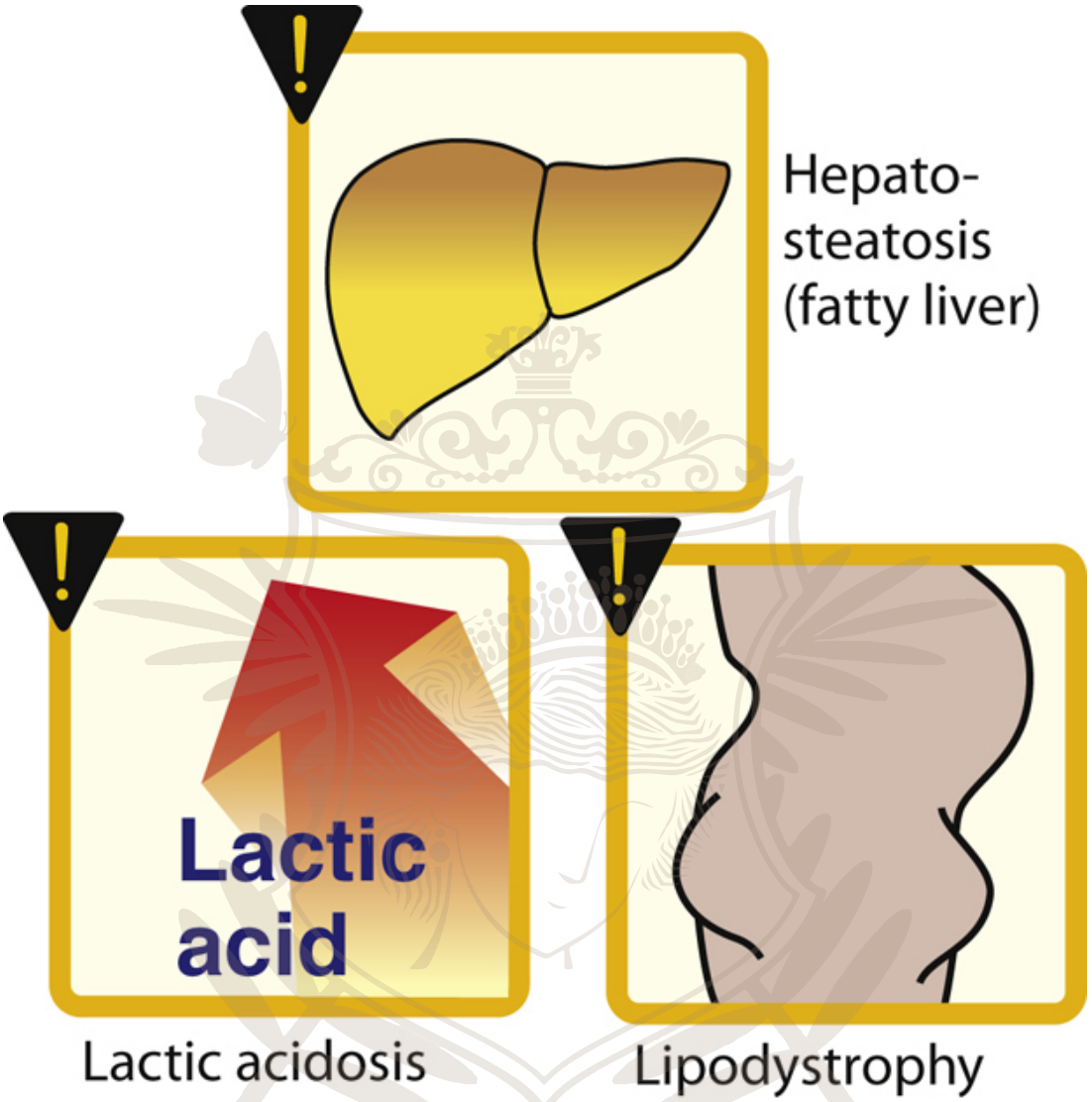

Figure 34.18 Some adverse reactions of nucleoside analogs.

4.Drug interactions: Due to the renal excretion of the NRTIs, there are not many drug interactions encountered with these agents except for *zidovudine* and *tenofovir*.

5.Resistance: NRTI resistance is well characterized, and the most common resistance pattern is a mutation at viral RT codon 184, which confers a high degree of resistance to *lamivudine* and *emtricitabine* but, more importantly, restores sensitivity to *zidovudine* and *tenofovir.* Because cross-resistance and antagonism occur between agents of the same analog class

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(thymidine, cytosine, guanosine, and adenosine), concomitant use of agents with the same analog target is contraindicated (for example, *lamivudine* and *emtricitabine* are both analogs of cytosine and should not be used together).

IX. NNRTIS USED TO TREAT HIV INFECTION

NNRTIs are highly selective, noncompetitive inhibitors of HIV RT. They bind to HIV RT at an allosteric hydrophobic site adjacent to the active site, inducing a conformational change that results in enzyme inhibition. They do not require activation by cellular enzymes. These drugs have common characteristics that include cross-resistance with other NNRTIs, drug interactions, and a high incidence of hypersensitivity reactions, including rash. The NNRTIs include *nevirapine* [ne-VYE-ra-peen], *efavirenz* [e-FA-veer-enz], *etravirine* [et-ra-VYE-rine], *rilpivirine* [ril-pi-VIR-een], and *doravirine* [DOR-a-VIR-een]. *Efavirenz* (Figure 34.19), *rilpivirine*, and *doravirine* are recommended in initial antiretroviral regimens in certain clinical situations. For example, *efavirenz* is safe to use in patients coinfected with tuberculosis because of its lower potential for drug interactions with rifamycins, and *rilpivirine* has the smallest tablet size, making it ideal for patients with difficulty swallowing. *Doravirine* has central nervous system tolerability advantages over *efavirenz* and fewer potential drug interactions than *efavirenz* or *rilpivirine.* And, unlike with *rilpivirine*, the virologic efficacy of *doravirine* is not compromised in patients with high HIV RNA levels and low CD4 counts. *Etravirine* is a second-generation NNRTI active against many HIV strains that are resistant to the first-generation NNRTIs; its use is limited to HIV treatment–experienced, multidrug-resistant patients who have evidence of ongoing viral replication. *Nevirapine* is rarely used due to toxicities and/or inferior antiviral efficacy.

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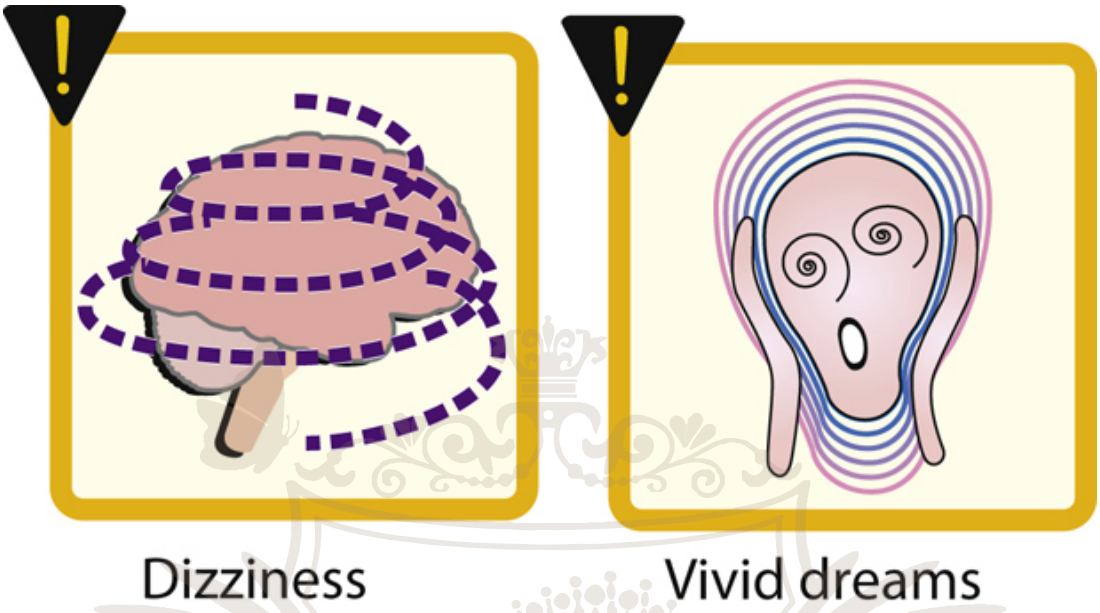

Figure 34.19 Adverse reactions of *efavirenz*.

X. PIS USED TO TREAT HIV INFECTION

Inhibitors of HIV protease have significantly altered the course of this devastating viral disease. Shortly after their introduction, the number of deaths in the United States due to AIDS decreased and continues to remain on the decline (Figure 34.20). Available PIs include *atazanavir* (ATV) [at-a-za-NA-veer], *darunavir* (DRV) [da-ROON-a-veer], *fosamprenavir* (FPV) [FOS-am-PREN-a-veer], *lopinavir* (LPV) [loe-PIN-a-vir], *nelfinavir* (NFV) [nel-FIN-a-veer], *saquinavir* (SQV) [sa-KWIN-a-veer], and *tipranavir* (TPV) [tip-RA-na-veer]. However, current HIV guidelines only list a select few (for example, *atazanavir* or *darunavir*) due to improved adverse effect profile, virologic efficacy, and ease of dosing. Due to their high genetic barrier to resistance, PIs are recommended in initial regimens in certain clinical situations (for example, patients with uncertain adherence or when resistance testing results are not yet available).

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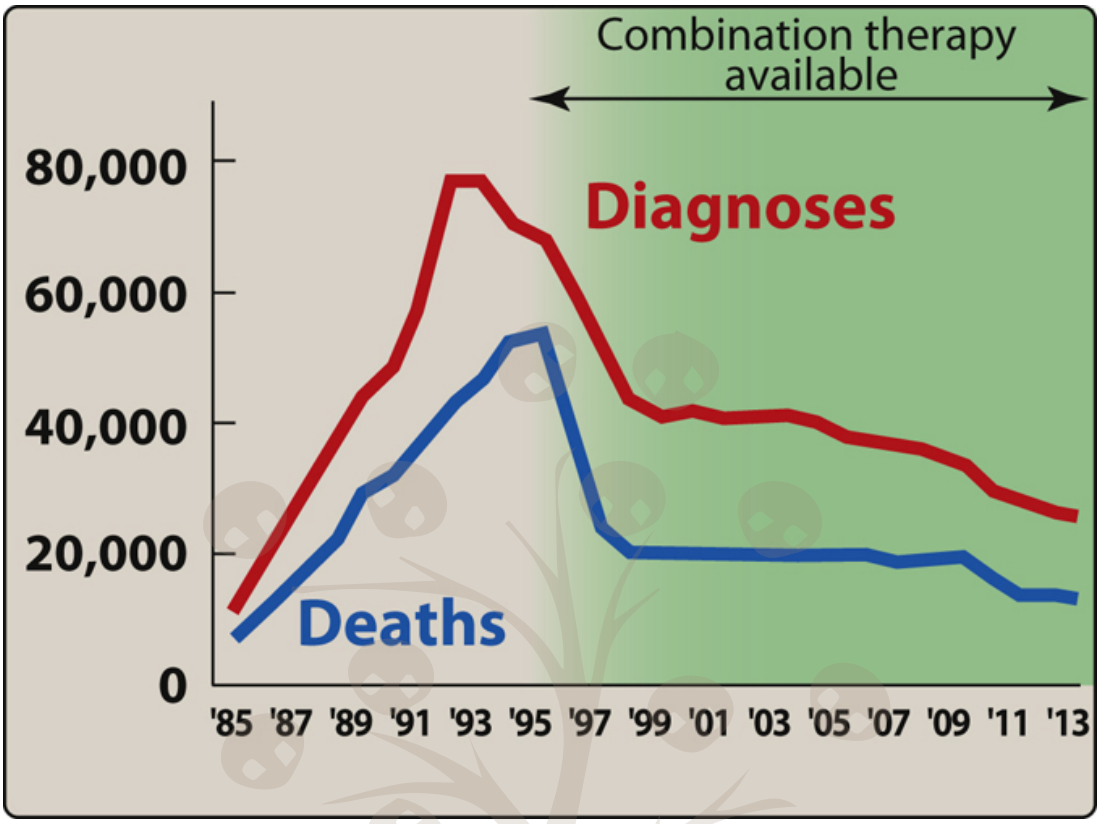

Figure 34.20 Estimated number of AIDS cases and deaths due to AIDS in the United States.*Green* background indicates years in which combination antiretroviral therapy came into common usage.

A. Overview of PIs

These potent agents have several common features that characterize their pharmacology.

1.Mechanism of action: Drugs in this group are reversible inhibitors of the HIV aspartyl protease (retropepsin), which is the viral enzyme responsible for cleavage of the viral polyprotein into a number of essential enzymes (RT, protease, and integrase) and several structural proteins. The inhibition prevents maturation of the viral particles and results in the production of noninfectious virions.

2.Pharmacokinetics: High-fat meals substantially increase the bioavailability of some PIs, such as *nelfinavir* and *saquinavir*, whereas the bioavailability of others is essentially unaffected. The

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HIV PIs are all substantially bound to plasma proteins. These agents are substrates for the CYP3A4 isoenzyme, and individual PIs are also metabolized by other CYP450 isoenzymes. Metabolism is extensive, and very little drug is excreted unchanged in urine.

3.Adverse effects: PIs commonly cause nausea, vomiting, and diarrhea (Figure 34.21). Disturbances in glucose and lipid metabolism also occur, including diabetes, hypertriglyceridemia, and hypercholesterolemia. Chronic administration results in fat redistribution, including loss of fat from the extremities, fat accumulation in the abdomen and the base of the neck ("buffalo hump"; Figure 34.22), and breast enlargement. These physical changes may indicate to others that an individual is HIV infected.

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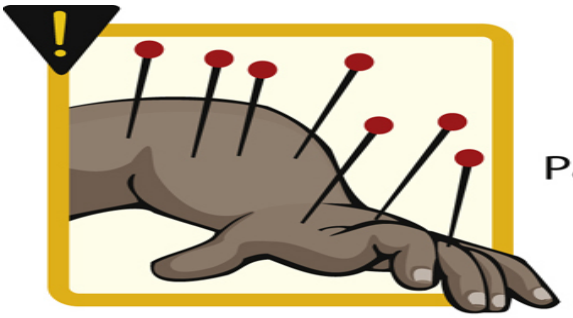

Paresthesias

Diarrhea

Nausea and vomiting

Hyper-triglyceridemia

Hyper-glycemia

Hyper-cholesterolemia

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Figure 34.21 Some adverse effects of the human immunodeficiency virus protease inhibitors.

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Figure 34.22 Accumulation of fat at the base of the neck in a patient receiving a protease inhibitor.

4.Drug interactions: Drug interactions are a common problem for PIs because they are substrates and also potent inhibitors of

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CYP450 isoenzymes. Drugs that rely on metabolism for their termination of action may accumulate to toxic levels. Examples of potentially dangerous interactions with PIs include rhabdomyolysis from *simvastatin* or *lovastatin*, excessive sedation from *midazolam* or *triazolam*, and respiratory depression from *fentanyl* (Figure 34.23). Other drug interactions that require dosage modification and cautious use include *warfarin, sildenafil,* and *phenytoin* (Figure 34.24). In addition, inducers of CYP450 isoenzymes may decrease PI plasma concentrations to suboptimal levels, contributing to treatment failures. Thus, drugs such as *rifampin* and *St. John's wort* are also contraindicated with PIs.

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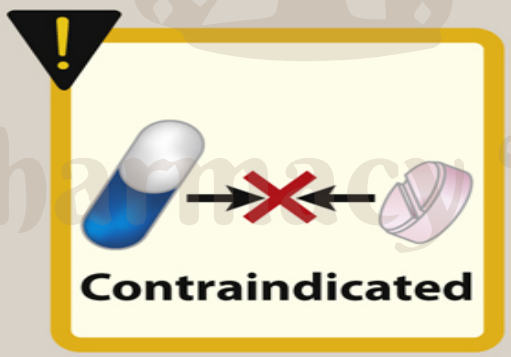
DRUG CLASS	EXAMPLE
ANTIARRHYTHMICS	*Amiodarone*
ERGOT DERIVATIVES	*Ergotamine*
ANTIMYCOBACTERIAL DRUGS	*Rifampin*
BENZODIAZEPINES	*Triazolam*
INHALED STEROIDS	*Fluticasone*
HERBAL SUPPLEMENTS	*St. John's wort*
HMG CoA REDUCTASE INHIBITORS	*Lovastatin* *Simvastatin*
NARCOTICS	*Fentanyl*
β2 AGONIST	*Salmeterol*



PROTEASE INHIBITORS

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Figure 34.23 Drugs that should not be coadministered with any protease inhibitor.

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DRUG CLASS	EXAMPLE
ANTICOAGULANTS	*Warfarin*
ANTICONVULSANTS	*Phenytoin*
ANTIFUNGALS	*Voriconazole*
ANTIMYCOBACTERIALS	*Rifabutin*
ERECTILE DYSFUNCTION AGENTS	*Sildenafil* *Tadalafil* *Vardenafil*
LIPID-LOWERING AGENTS	*Atorvastatin*
NARCOTICS	*Methadone*

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PROTEASE INHIBITORS

A L G r a w a n y

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Figure 34.24 Drugs that require dose modifications or cautious use with any protease inhibitor.

5.Resistance: Resistance occurs as an accumulation of stepwise mutations of the protease gene. Initial mutations result in decreased ability of the virus to replicate, but as the mutations accumulate, virions with high levels of resistance to the PIs emerge. Suboptimal concentrations of PI result in the more rapid appearance of resistant strains.

B. Atazanavir

Atazanavir is well absorbed after oral administration. It must be taken with food to increase absorption and bioavailability. *Atazanavir* requires an acidic environment for absorption. Thus, unboosted *atazanavir* is contraindicated with concurrent use of proton pump inhibitors, and administration must be spaced apart from H_2 blockers and antacids. *Atazanavir* can be boosted by *ritonavir* or *cobicistat.* The drug is highly protein bound and undergoes extensive metabolism by CYP3A4 isoenzymes. It is excreted primarily in bile. It has a half-life of about 7 hours, but it may be administered once daily. *Atazanavir* is a competitive inhibitor of glucuronyl transferase, and benign hyperbilirubinemia and jaundice are known adverse effects. In addition, the drug may prolong the PR interval. *Atazanavir* exhibits a decreased risk of hyperlipidemia compared with other PIs.

C. Darunavir

Darunavir is coadministered with *cobicistat* or a low dose of *ritonavir. Darunavir* is approved for initial therapy in treatment-naïve HIV-infected patients, as well as for treatment-experienced patients with HIV resistant to other PIs. *Darunavir* must be taken with food to increase absorption. The elimination half-life is 15 hours when combined with *ritonavir. Darunavir* is extensively metabolized by the CYP3A enzymes and is also an inhibitor of the CYP3A4 isoenzyme. Adverse effects are similar to those of the other PIs. In addition, *darunavir* therapy has been associated with a rash.

A summary of PIs is presented in Figure 34.25.

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DRUGS	MAJOR TOXICITIES AND CONCERNS
Atazanavir	Nausea, abdominal discomfort, skin rash, hyperbilirubinemia
Darunavir	Nausea, abdominal discomfort, headache, skin rash
Fosamprenavir	Nausea, diarrhea, vomiting, oral and perioral paresthesia, and rash
Lopinavir	Gastrointestinal, hyper-lipidemia, insulin resistance
Nelfinavir	Diarrhea, nausea, flatulence, rash
Ritonavir	Diarrhea, nausea, taste perversion, vomiting, anemia, increased hepatic enzymes, increased triglycerides. Capsules require refrigeration, tablets do not. Take with meals; chocolate milk improves the taste.
Saquinavir	Diarrhea, nausea, abdominal discomfort, elevated trans-aminase levels. Take with high-fat meal or within 2 hours of a full meal.
Tipranavir	Nausea, vomiting, diarrhea, rash, severe hepatotoxicity, intracranial hemorrhage

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Figure 34.25 Summary of protease inhibitors.[Note: *Lopinavir* is coformulated with *ritonavir. Ritonavir* inhibits the metabolism of *lopinavir*, thereby increasing its level in the plasma.]

XI. ENTRY INHIBITORS

The HIV entry process involves a sequential and coordinated interaction between the virus and the host cell that includes three key steps: (1) attachment of HIV glycoprotein 120 with the host CD4 receptor; (2) binding of HIV glycoprotein 120 with the host chemokine coreceptor; and (3) glycoprotein 41–mediated fusion of HIV with the host surface membrane. The HIV entry inhibitor drug class includes three subclasses: (1) attachment inhibitors, (2) CCR5 coreceptor antagonists, and (3) fusion inhibitors.

A. Fostemsavir

Fostemsavir [fos-TEM-sa-vir], a prodrug that is hydrolyzed to the active drug temsavir, exerts its mechanism of action by binding to HIV envelope glycoprotein 120 and inhibiting attachment. Temsavir binding to glycoprotein 120 prevents the conformational change required for attachment to the host CD4 cell surface receptor. In the absence of effective attachment of HIV glycoprotein 120 with the host CD4 receptor, HIV does not enter the host cell. *Fostemsavir* is indicated in heavily treatment-experienced adults with multidrug-resistant HIV failing the current antiretroviral regimen. The drug is dosed orally twice daily. It is a CYP450 substrate and coadministration with strong CYP450 inducers is contraindicated. The most common adverse effect is nausea.

B. Ibalizumab

Ibalizumab [eye-ba-LIZ-ue-mab] inhibits post-CD4 attachment events required for HIV entry. It selectively binds to an epitope on the domain 2 of the CD4 receptor inducing conformational changes that ultimately prevent the interaction of viral glycoprotein 120 and HIV coreceptors. *Ibalizumab* is not often used because it is indicated for heavily treatment-experienced adult patients with multidrug-resistant HIV. It is

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administered every 14 days as an IV infusion. The most common adverse event reported is diarrhea.

C. Maraviroc

Maraviroc [ma-RAV-i-rok] is an entry inhibitor that blocks the CCR5 coreceptor that works with gp41 to facilitate HIV entry through the membrane into the cell. HIV may express preference for either the CCR5 coreceptor or the CXCR4 coreceptor, or both (dual tropic). Prior to use of *maraviroc*, a test to determine viral tropism is required to distinguish whether the strain of HIV virus uses the CCR5 coreceptor, the CXCR4 coreceptor, or is dual tropic. Only strains of HIV that use CCR5 to gain access to the cell can be successfully treated with *maraviroc.* The drug is well absorbed after oral administration. *Maraviroc* is metabolized mainly by the hepatic CYP3A isoenzyme, and the dose must be reduced when given with most PIs or strong CYP450 inhibitors. Conversely, it should be increased in patients receiving *efavirenz*, *etravirine*, or strong CYP450 inducers. *Maraviroc* is generally well tolerated. The drug has been associated with severe hepatotoxicity, which may be preceded by a fever or rash. Monitoring of liver function is recommended.

D. Enfuvirtide

Enfuvirtide [en-FYOO-vir-tide] is a fusion inhibitor. For HIV to gain entry to the host cell, it must fuse its membrane with that of the host cell. This is accomplished by changes in the conformation of the viral transmembrane glycoprotein gp41, which occurs when HIV binds to the host cell surface. *Enfuvirtide* is a polypeptide that binds to gp41, preventing the conformational change. *Enfuvirtide*, in combination with other antiretroviral agents, is indicated for therapy of treatment-experienced patients with evidence of viral replication despite ongoing antiretroviral drug therapy. As a peptide, it must be given subcutaneously. Most of the adverse effects are related to the injection, including pain, erythema, induration, and nodules, which occur in almost all patients. *Enfuvirtide* must be reconstituted prior to administration.

XII. INTEGRASE INHIBITORS

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Raltegravir [ral-TEG-ra-veer], *elvitegravir* [el-vi-TEG-ra-vir], *dolutegravir* [doe-loo-TEG-ra-vir], *bictegravir* [bik-TEG-ra-vir], and *cabotegravir* [KA-boe-TEG-ra-vir] are integrase strand transfer inhibitors (INSTIs), often called integrase inhibitors. These agents work by inhibiting the insertion of proviral DNA into the host cell genome. The active site of the integrase enzyme binds to the host cell DNA and includes two divalent metal cations that serve as chelation targets for the INSTIs. As a result, when an INSTI is present, the active site of the enzyme is occupied and the integration process is halted. Long-acting injectable *cabotegravir* in combination with *rilpivirine* is indicated for HIV treatment, while long-acting injectable *cabotegravir* alone is used for preexposure prophylaxis in individuals at high risk for HIV acquisition. The half-life of *elvitegravir* is 3 hours when administered alone, but increases to approximately 9 hours when boosted by *cobicistat.* Pharmacokinetic boosting of *elvitegravir* allows once-daily dosing with food. The INSTIs are generally well tolerated, with nausea and diarrhea being the most commonly reported adverse effects. Importantly, oral INSTIs are subject to chelation interactions with antacids, resulting in significant reductions in bioavailability. Therefore, oral INSTI doses should be separated from antacids and other polyvalent cations by several hours. Resistance to INSTIs occurs with mutations within the integrase gene. Cross-resistance between *raltegravir* and *elvitegravir* can occur, although *dolutegravir* and *bictegravir* have limited cross-resistance to other INSTIs.

Clinical Application 34.1: Choosing Among Integrase Strand Transfer Inhibitors

Integrase strand transfer inhibitors (INSTIs) are a mainstay of initial treatment for HIV infection. Recommended initial regimens for most patients with HIV include one of two INSTIs (*dolutegravir* or *bictegravir*) plus two nucleoside reverse transcriptase inhibitors or *dolutegravir/lamivudine.* For most patients, these INSTI-containing regimens are highly effective and have relatively infrequent adverse effects and few drug interactions. When choosing among the INSTIs, there are key differences in dosing, drug interactions, emergence of resistance at virologic failure, effect on renal function, and adverse events. The advantages of *bictegravir* are that it is dosed once daily, is coformulated with *emtricitabine/tenofovir alafenamide* as part of a complete initial regimen, has a high genetic barrier to resistance, and has no food requirements. Disadvantages of *bictegravir* are that oral absorption is reduced by simultaneous administration with drugs or supplements containing polyvalent cations, it raises serum creatinine levels (~0.1 mg/dL) through inhibition of tubular secretion

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of creatinine, and it cannot be used with *rifampin.* Advantages of *dolutegravir* are that it is dosed once daily; is coformulated with *lamivudine* with or without *abacavir* as part of a complete initial regimen; and has a high genetic barrier to resistance, no food requirements, and minimal CYP3A4 interactions. Disadvantages of *dolutegravir* are that it has drug interactions with polyvalent cations, it raises serum creatinine levels (~0.1-0.15 mg/dL) through inhibition of tubular secretion of creatinine, it has higher rates of insomnia and headache compared to other regimens, and, when coformulated with *abacavir*/*lamivudine*, it has a large tablet size among coformulated single-pill regimens. Additionally, data now suggest greater weight gain with certain INSTI-based regimens than with other antiretrovirals. Clinically, the choice between INSTIs is guided by the known advantages and disadvantages of each recommended agent.

XIII. PHARMACOKINETIC ENHANCERS

A. Ritonavir

Ritonavir [ri-TOE-na-veer] is no longer used as a single PI but, instead, is used as a pharmacokinetic enhancer or "booster" of other PIs. *Ritonavir* is a potent inhibitor of CYP3A, and concomitant *ritonavir* administration at low doses increases the bioavailability of the second PI, often allowing for longer dosing intervals. The resulting higher C_{min} levels of the "boosted" PI also help to prevent the development of HIV resistance. Therefore, "boosted" PIs are recommended for use in initial HIV regimens in certain clinical situations. Metabolism by CYP3A4 and CYP2D6 and biliary excretion are the primary methods of elimination. *Ritonavir* has a half-life of 3 to 5 hours. Although *ritonavir* is primarily an inhibitor of CYP450 isoenzymes, it may also induce several CYP450 isoenzymes, and numerous drug interactions have been identified.

B. Cobicistat

Cobicistat [koe-BIK-i-stat] is a pharmacokinetic enhancer or booster drug used in combination treatments for HIV. This agent inhibits CYP3A isoenzymes and is used to enhance the bioavailability of the PIs *atazanavir* and *darunavir*, and the integrase inhibitor *elvitegravir.* Because *cobicistat* inhibits CYP3A, CYP2D6, and the transporter P-gp, numerous drug interactions exist. *Cobicistat* may also cause

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elevations in serum creatinine due to inhibition of tubular creatinine secretion.

Chapter Summary

- Viruses are unable to carry out metabolic processes on their own and can only replicate within the living cell of a host organism. A few viruses respond to available antiviral drugs and some antiviral agents can be employed prophylactically.
- Influenza A and B are respiratory viral infections commonly treated with the neuraminidase inhibitors *oseltamivir*, *zanamivir*, *and peramivir.* These drugs have various routes of administration and must be administered within 48 hours after the onset of influenza symptoms. They can also be administered as postexposure prophylaxis in patients following contact with an individual who has influenza.
- HBV involves replication in and destruction of hepatocytes and is commonly treated with oral therapy including the nucleos(t)ide analogs *tenofovir* or *entecavir. Pegylated interferon alfa-2a* can also be used to treat hepatitis B, but its use may be limited by the need for subcutaneous injections and side effects including flu-like symptoms.
- HCV primarily affects the liver and is treated with a combination of oral DAA agents targeting different stages of the viral life cycle. Effective combinations include one or more drugs from at least two of the following drug classes: NS3/NS4A PIs, NS5B polymerase inhibitors, and NS5A replication complex inhibitors.
- Herpes viruses are associated with a broad spectrum of diseases and there are several antiviral medications available to treat them. Apart from *foscarnet* and *cidofovir*, all are nucleoside analogs. *Acyclovir* is the prototype of a group of antiviral agents that are activated by viral thymidine kinase to become inhibitors of viral DNA polymerase, blocking viral DNA synthesis. *Acyclovir*, *famciclovir*, and *valacyclovir* are used to treat most cases of HSV types 1 and 2.
- HIV is treated with a combination of drugs from among five available classes: NRTIs, NNRTIs, PIs, integrase inhibitors, and entry inhibitors. Pharmacokinetic enhancers are also available and serve to increase drug levels of select concomitantly administered antiretroviral agents.
- Initial therapy for HIV consists of a combination of two NRTIs with an integrase inhibitor, an NNRTI, or a PI.

STUDY QUESTIONS

Choose the ONE best answer.

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34.1 Which of the following medications is administered via intravenous injection for treatment of influenza?

A. Oseltamivir
B. Peramivir
C. Zanamivir
D. Baloxavir marboxil

Correct answer = B. Peramivir is administered intravenously. Oseltamivir and baloxavir marboxil are administered orally. Zanamivir is administered via inhalation.

34.2 A 24-year-old woman is diagnosed with genital herpes simplex virus infection. Which of the following agents is indicated for use in this diagnosis?

A. Valacyclovir
B. Cidofovir
C. Ganciclovir
D. Zanamivir

Correct answer = A. Valacyclovir, famciclovir, penciclovir, and acyclovir are all indicated for herpes simplex virus infection. Cidofovir and ganciclovir are used for CMV retinitis. Zanamivir is indicated for influenza.

34.3 A woman who is being treated for chronic hepatitis B develops Fanconi syndrome (generalized proximal tubule dysfunction) while on treatment. Which of the following medications is most likely included in her HBV treatment?

A. Entecavir
B. Ribavirin
C. Lamivudine
D. Tenofovir disoproxil fumarate

Correct answer = D. Fanconi syndrome nephrotoxicity can be seen with tenofovir disoproxil fumarate. This adverse effect is uncommon with lamivudine and entecavir. Ribavirin is used for the treatment of hepatitis C infection (not HBV).

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34.4 Which class of direct-acting antivirals for hepatitis C works by inhibiting formation of the membranous web that provides a platform for viral replication?

A. NS3/NS4A protease inhibitors
B. NS5B polymerase inhibitors
C. NS5A replication complex inhibitors
D. Interferons

Correct answer = C. NS5A inhibitors work to inhibit the formation of proteins that form a membranous web, which serves as a platform for viral replication. NS3/NS4A protease inhibitors prevent processing of the single polyprotein encoded by HCV RNA into individually active proteins. NS5B polymerase inhibitors act on the RNA polymerase responsible for HCV replication. The mechanism of interferons has not been fully defined.

34.5 A 59-year-old man with hepatitis C genotype 1 infection, who is treatment naïve and noncirrhotic, presents for treatment initiation. He has a past medical history significant for gastroesophageal reflux disease and is prescribed oral omeprazole 40 mg once daily. Which of the following is the best treatment option?

A. Pegylated interferon and ribavirin
B. Sofosbuvir
C. Glecaprevir/pibrentasvir
D. Sofosbuvir/ledipasvir

Correct answer = C. Treatment-naïve, noncirrhotic patients with genotype 1 infection can be treated with the combination of glecaprevir/pibrentasvir. Sofosbuvir monotherapy is incorrect because hepatitis C treatment consists of a combination of direct-acting antivirals. Pegylated interferon and ribavirin regimens are no longer recommended due to the availability of more effective treatments with fewer side effects. Sofosbuvir/ledipasvir is incorrect because of a drug interaction with the omeprazole.

34.6 A 30-year-old man with human immunodeficiency virus infection is being treated with an antiretroviral regimen. Four weeks after initiating therapy, he presents to the emergency department complaining of fever, rash, and gastrointestinal upset. His HLA-

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B*5701 test is positive. Which of the following drugs is most likely the cause of his symptoms?

A. Zidovudine
B. Abacavir
C. Efavirenz
D. Darunavir

Correct answer = B. The abacavir hypersensitivity reaction is characterized by fever, rash, and gastrointestinal upset. The patient must stop therapy and should not be rechallenged with abacavir.

34.7 A 62-year-old man with human immunodeficiency virus infection is being treated with an antiretroviral regimen containing elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate and has achieved a sustained undetectable level of HIV RNA. His prescriber would like to change his therapy to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide. Which of the following information should the prescriber provide to the patient that best summarizes the advantage of tenofovir alafenamide over tenofovir disoproxil fumarate?

A. Removal of food restrictions
B. Fewer drug interactions
C. Twice-daily dosing
D. Improved renal and bone safety profile

Correct answer = D. Tenofovir alafenamide delivers the same active drug as tenofovir disoproxil fumarate, but with a lower incidence of renal and bone adverse effects. Both tenofovir-containing combinations are dosed once daily and should be taken with food. No change in drug interactions is expected, since tenofovir alafenamide is a prodrug that, like TDF, is metabolized to tenofovir.

34.8 Which of the following HIV antiretrovirals is an orally administered entry inhibitor?

A. Maraviroc
B. Enfuvirtide
C. Ibalizumab

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D. Raltegravir

Correct answer = A. Maraviroc and fostemsavir are the only orally administered entry inhibitors for HIV infection. Enfuvirtide is an entry inhibitor (fusion inhibitor), but it is injected subcutaneously. Ibalizumab is an entry inhibitor (attachment inhibitor), but is administered via intravenous infusion. Raltegravir is an INSTI for HIV infection.

34.9 A 64-year-old treatment-experienced man with human immunodeficiency virus infection is receiving an antiretroviral regimen containing atazanavir. Which of the following concomitant medications should be avoided?

A. Metoprolol
B. Pravastatin
C. Metronidazole
D. Omeprazole

Correct answer = D. Atazanavir requires an acidic environment for optimal absorption. In treatment-experienced patients, combination therapy with proton pump inhibitors (such as omeprazole) is contraindicated. There are no known or anticipated drug interactions between atazanavir and metoprolol, pravastatin, or metronidazole.

34.10 A 55-year-old man is admitted to the hospital for management of severe symptoms of SARS-CoV-2 (COVID-19) infection. Which of the following is most appropriate to include in the treatment regimen?

A. Entecavir
B. Famciclovir
C. Peramivir
D. Remdesivir

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Correct answer = D. Remdesivir is an adenosine analog that inhibits SARS-CoV-2 RNA–dependent RNA polymerase, resulting in disruption of viral replication in COVID-19. Entecavir is a guanosine nucleoside analog for the treatment of HBV infection. Famciclovir is indicated for the treatment of herpes simplex virus, and peramivir is used in the treatment of influenza.

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35

Antiprotozoal Drugs

Marylee V. Worley, Jonathan C. Cho

I. OVERVIEW

Protozoan parasites that cause human diseases are prevalent in underdeveloped tropical and subtropical countries, where sanitary conditions, hygienic practices, and control of the vectors of transmission are inadequate. However, with increased world travel, protozoal diseases are no longer confined to specific geographic locales. Because they are unicellular eukaryotes, the protozoal cells have metabolic processes closer to those of the human host than to prokaryotic bacterial pathogens. Therefore, protozoal diseases are less easily treated than bacterial infections, and many of the antiprotozoal drugs cause serious toxic effects in the host, particularly on cells showing high metabolic activity. Most antiprotozoal agents have not proven to be safe for pregnant patients. Drugs used to treat protozoal infections are listed in Figure 35.1. [Note: Some of the drugs discussed below are not available in the United States; however, most can be obtained by contacting the Centers for Disease Control and Prevention.]

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AMEBIASIS

Chloroquine ARALEN
Iodoquinol YODOXIN
Metronidazole FLAGYL
Paromomycin GENERIC ONLY
Tinidazole TINDAMAX

MALARIA

Artemether/lumefantrine COARTEM
Artesunate GENERIC ONLY
Atovaquone-proguanil MALARONE
Chloroquine ARALEN
Mefloquine LARIAM
Primaquine GENERIC ONLY
Pyrimethamine DARAPRIM
Quinine QUALAQUIN
Tafenoquine ARAKODA, KRINTAFEL

BABESIOSIS

Atovaquone MEPRON
Quinine QUALAQUIN

TRYPANOSOMIASIS

Benznidazole GENERIC ONLY
Eflornithine GENERIC ONLY
Melarsoprol GENERIC ONLY
Nifurtimox LAMPIT
Pentamidine NEBUPENT, PENTAM
Suramin GERMANIN

LEISHMANIASIS

Miltefosine IMPAVIDO
Sodium stibogluconate

TOXOPLASMOSIS

Pyrimethamine DARAPRIM

GIARDIASIS

Metronidazole FLAGYL
Nitazoxanide ALINIA
Tinidazole TINDAMAX

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Figure 35.1 Summary of antiprotozoal agents.

II. CHEMOTHERAPY FOR AMEBIASIS

Amebiasis (amebic dysentery) is an infection of the intestinal tract caused by Entamoeba histolytica. E. histolytica is endemic in developing countries and is mainly transmitted via the fecal–oral route or through ingestion of contaminated food or water. Most infected individuals are asymptomatic but can exhibit varying degrees of illness depending on host factors and formation of trophozoites. The diagnosis is established by isolating E. histolytica from feces. Due to the risk of developing invasive disease and acting as a potential source of infection for others, therapy is indicated for acutely ill patients and asymptomatic carriers of *E. histolytica.* A summary of the life cycle of E. histolytica is presented in Figure 35.2. Therapeutic agents for amebiasis are classified as luminal, systemic, or mixed amebicides according to the site of action (Figure 35.2). For example, luminal amebicides act on the parasite in the lumen of the bowel, whereas systemic amebicides are effective against amebas in the intestinal wall and liver. Mixed amebicides are effective against both the luminal and systemic forms of the disease, although luminal concentrations are too low for single-drug treatment.

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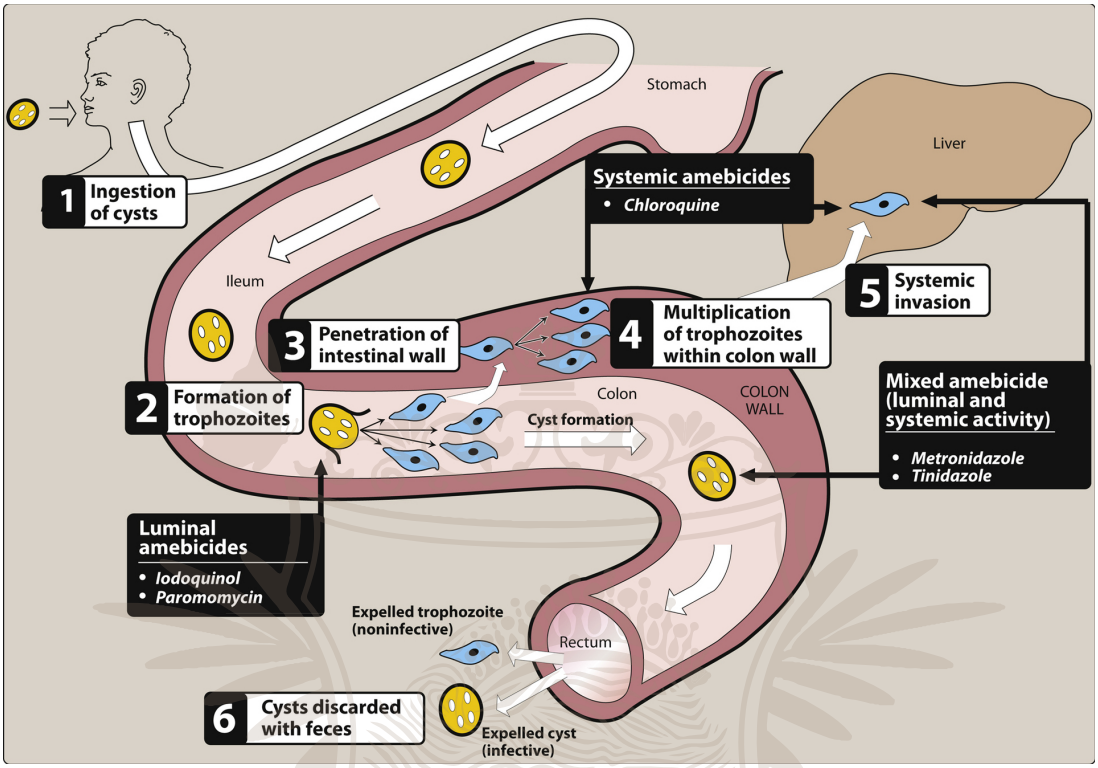

Figure 35.2 Life cycle of *Entamoeba histolytica*, showing the sites of action of amebicidal drugs.

A. Mixed amebicides

1. Metronidazole: *Metronidazole* [me-troe-NYE-da-zole], a nitroimidazole, is the mixed amebicide of choice for treating amebic infections. [Note: *Metronidazole* is also used in the treatment of infections caused by Giardia lamblia, Trichomonas vaginalis, anaerobic cocci, anaerobic gram-negative bacilli (for example, Bacteroides species), and anaerobic, gram-positive bacilli (for example, Clostridioides difficile).]

a. Mechanism of action: Amebas possess ferredoxin-like, low–redox potential, electron transport proteins that participate in metabolic electron removal reactions. The nitro group of *metronidazole* is able to serve as an electron acceptor, forming reduced cytotoxic

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compounds that bind to proteins and deoxyribonucleic acid (DNA), resulting in death of the E. histolytica trophozoites.

b. Pharmacokinetics: *Metronidazole* is completely and rapidly absorbed after oral administration. [Note: For the treatment of amebiasis, *metronidazole* therapy is usually followed by administration of a luminal amebicide, such as *iodoquinol* or *paromomycin.* This combination provides cure rates of greater than 90%.] *Metronidazole* distributes well throughout body tissues and fluids. Therapeutic levels can be found in vaginal and seminal fluids, saliva, breast milk, and cerebrospinal fluid (CSF). Metabolism of the drug depends on hepatic oxidation of the *metronidazole* side chain by mixed-function oxidase, followed by glucuronidation. The drug accumulates in patients with severe hepatic disease. The parent drug and its metabolites are excreted in the urine.

c. Adverse effects: The most common adverse effects are nausea, vomiting, epigastric distress, and abdominal cramps (Figure 35.3). An unpleasant, metallic taste is commonly experienced. Other effects include oral moniliasis (yeast infection of the mouth) and, rarely, neurotoxicity (dizziness, vertigo, and numbness or paresthesia), which may necessitate discontinuation of the drug. *Metronidazole* may prolong the QT interval. It should be used with caution in patients taking concurrent drugs that increase the risk of QT prolongation. If taken with alcohol, a *disulfiram*-like reaction may occur (see Chapter 47).

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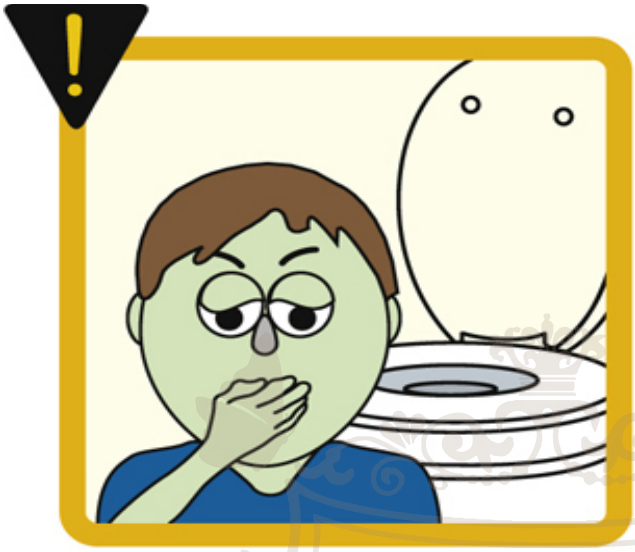
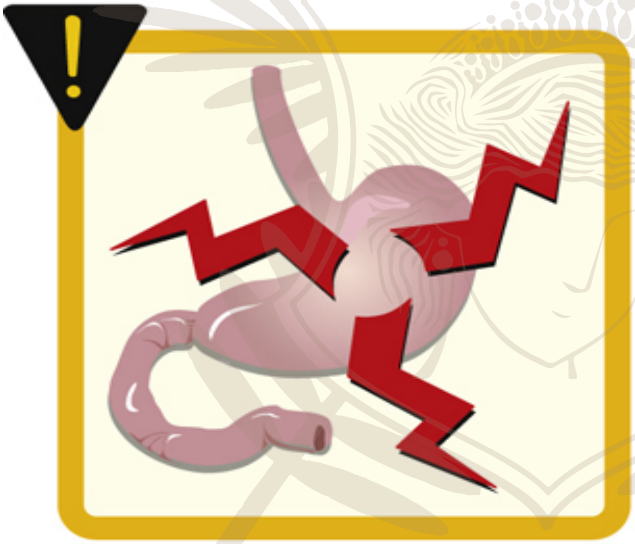
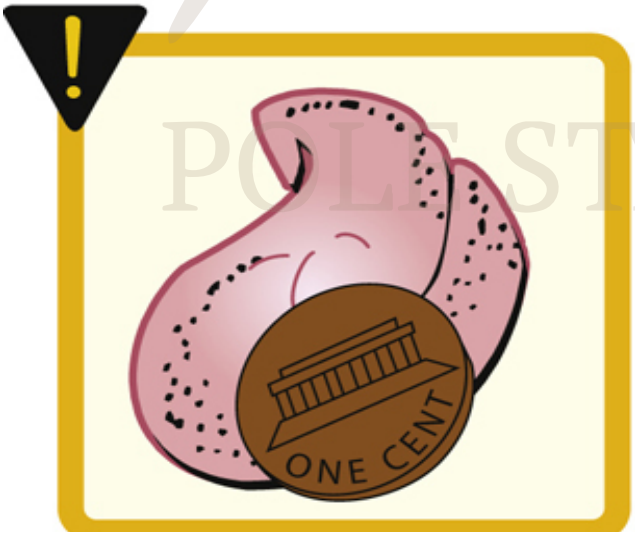


Nausea



GI disturbance



Metallic taste

POLE STAR

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Figure 35.3 Adverse effects of *metronidazole*.GI = gastrointestinal.

2.Tinidazole: *Tinidazole* [tye-NI-da-zole] is a second-generation nitroimidazole that is similar to *metronidazole* in the spectrum of activity and absorption. It is used for treatment of amebiasis, amebic liver abscess, giardiasis, and trichomoniasis. *Tinidazole* is as effective as *metronidazole*, but it is more expensive. It is metabolized by CYP3A4, and strong inducers or inhibitors of CYP3A4 may reduce or increase *tinidazole* concentrations, respectively. Adverse effects include gastrointestinal upset and metallic taste. Alcohol consumption should be avoided during therapy.

B. Luminal amebicides

After treatment of invasive intestinal or extraintestinal amebic disease is complete, a luminal agent, such as *iodoquinol*, *diloxanide furoate*, or *paromomycin*, should be administered for treatment of the asymptomatic colonization state.

1.Iodoquinol: *Iodoquinol* [eye-oh-doe-QUIN-ole], a halogenated 8-hydroxyquinoline, is amebicidal against E. histolytica and is effective against the luminal trophozoite and cyst forms. Adverse effects of *iodoquinol* include rash, diarrhea, and dose-related peripheral neuropathy, including a rare optic neuritis. Long-term use of this drug should be avoided.

2.Paromomycin: *Paromomycin* [par-oh-moe-MYE-sin], an aminoglycoside antibiotic, is only effective against the luminal forms of E. histolytica because it is not significantly absorbed from the gastrointestinal tract. *Paromomycin* is directly amebicidal and also exerts its antiamebic actions by reducing the population of intestinal flora. Gastrointestinal distress and diarrhea are the principal adverse effects.

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C. Systemic amebicides

The systemic amebicide *chloroquine* [KLOR-oh-kwin] is useful for treating extraintestinal amebiasis, such as liver abscesses, and intestinal wall infections caused by amebas. *Chloroquine* is used in combination with *metronidazole* (or as a substitute for one of the nitroimidazoles in the case of intolerance) to treat amebic liver abscesses. It eliminates trophozoites in liver abscesses, but it is not useful in treating luminal amebiasis. Therapy should be followed with a luminal amebicide. *Chloroquine* is also effective in the treatment of malaria.

A summary of the treatment of amebiasis is shown in Figure 35.4.

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CLINICAL SYNDROME	DRUG
Asymptomatic cyst carriers	*Iodoquinol* or *paromomycin*
Diarrhea/dysentery	*Metronidazole* plus *iodoquinol* or *paromomycin*
Amebic liver abscess	*Metronidazole* (or *tinidazole*) plus *iodoquinol* or *paromomycin*

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Figure 35.4 Some commonly used therapeutic options for the treatment of amebiasis.

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III. CHEMOTHERAPY FOR MALARIA

Malaria is an acute infectious disease caused by five species of the protozoal genus Plasmodium. It is transmitted to humans through the bite of a female Anopheles mosquito. The classic presentation of malaria begins with headache and fatigue, followed by fever, chills, and sweats. Plasmodium falciparum is the most dangerous species and the primary cause of severe malaria, causing an acute, rapidly fulminating disease characterized by persistent high fever, hyperparasitemia, and organ system dysfunction. P. falciparum infection can lead to capillary obstruction, cerebral malaria, and death within days without prompt treatment. Plasmodium vivax, Plasmodium malariae, and *Plasmodium ovale* cause a milder form of the disease; however, the P. vivax and P. ovale species can also remain dormant in the liver (hypnozoite stage), which can cause relapse months or years later. Plasmodium knowlesi is an uncommon form of malaria, previously thought to infect only nonhuman primates, which causes human infections, sometimes severe, in Southeast Asia. Resistance acquired by Plasmodium to antiprotozoal drugs has led to new therapeutic challenges, particularly in the treatment of P. falciparum. A summary of the life cycle of the parasite and the sites of action of the antimalarial drugs are presented in Figure 35.5.

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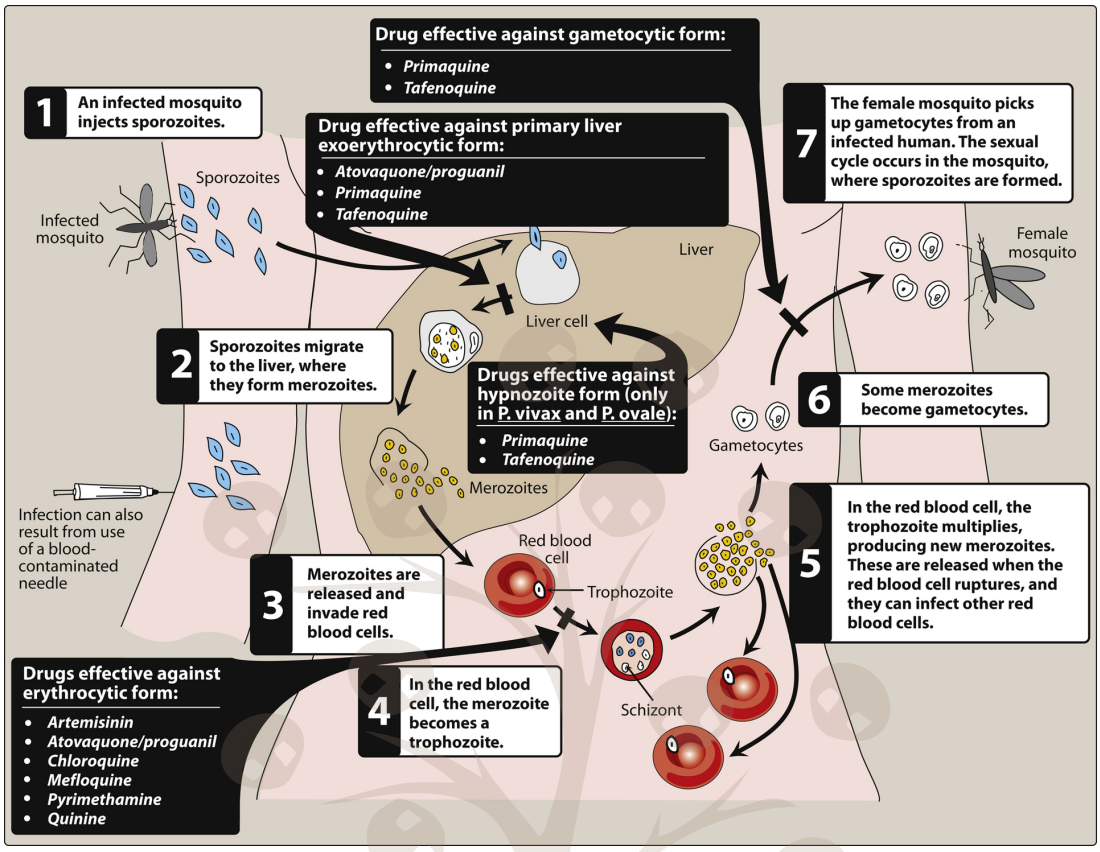

Figure 35.5 Life cycle of the malarial parasite, showing the sites of action of antimalarial drugs.

A. Primaquine

Primaquine [PRIM-a-kwin], an 8-aminoquinoline, is an oral antimalarial drug that eradicates primary exoerythrocytic (liver) forms of plasmodia and the hypnozoites of recurring malarias (P. vivax and P. ovale). The sexual (gametocytic) forms of all plasmodia are destroyed in the plasma or are prevented from maturing later in the mosquito, thereby interrupting transmission of the disease. [Note: *Primaquine* is not effective against the erythrocytic stage of malaria and, therefore, it cannot be used as monotherapy for treatment.]

1. Mechanism of action: While not completely understood, metabolites of *primaquine* are believed to act as oxidants that

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severely disrupt the metabolic processes of plasmodial mitochondria. The metabolites are responsible for the schizonticidal action, as well as for the hemolysis and methemoglobinemia encountered as toxicities.

2.Pharmacokinetics: *Primaquine* is well absorbed after oral administration and is not concentrated in tissues or erythrocytes. It is rapidly oxidized to many compounds, primarily the deaminated drug. Which compound possesses the schizonticidal activity has not been established. The drug is minimally excreted in the urine.

3.Adverse effects: *Primaquine* is associated with drug-induced hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency (Figure 35.6). Large doses of the drug may cause abdominal discomfort (especially when administered in combination with *chloroquine*) and occasional methemoglobinemia. *Primaquine* should not be used during pregnancy, and its use is contraindicated in patients with rheumatoid arthritis or systemic lupus erythematosus. All Plasmodium species may develop resistance to *primaquine*.

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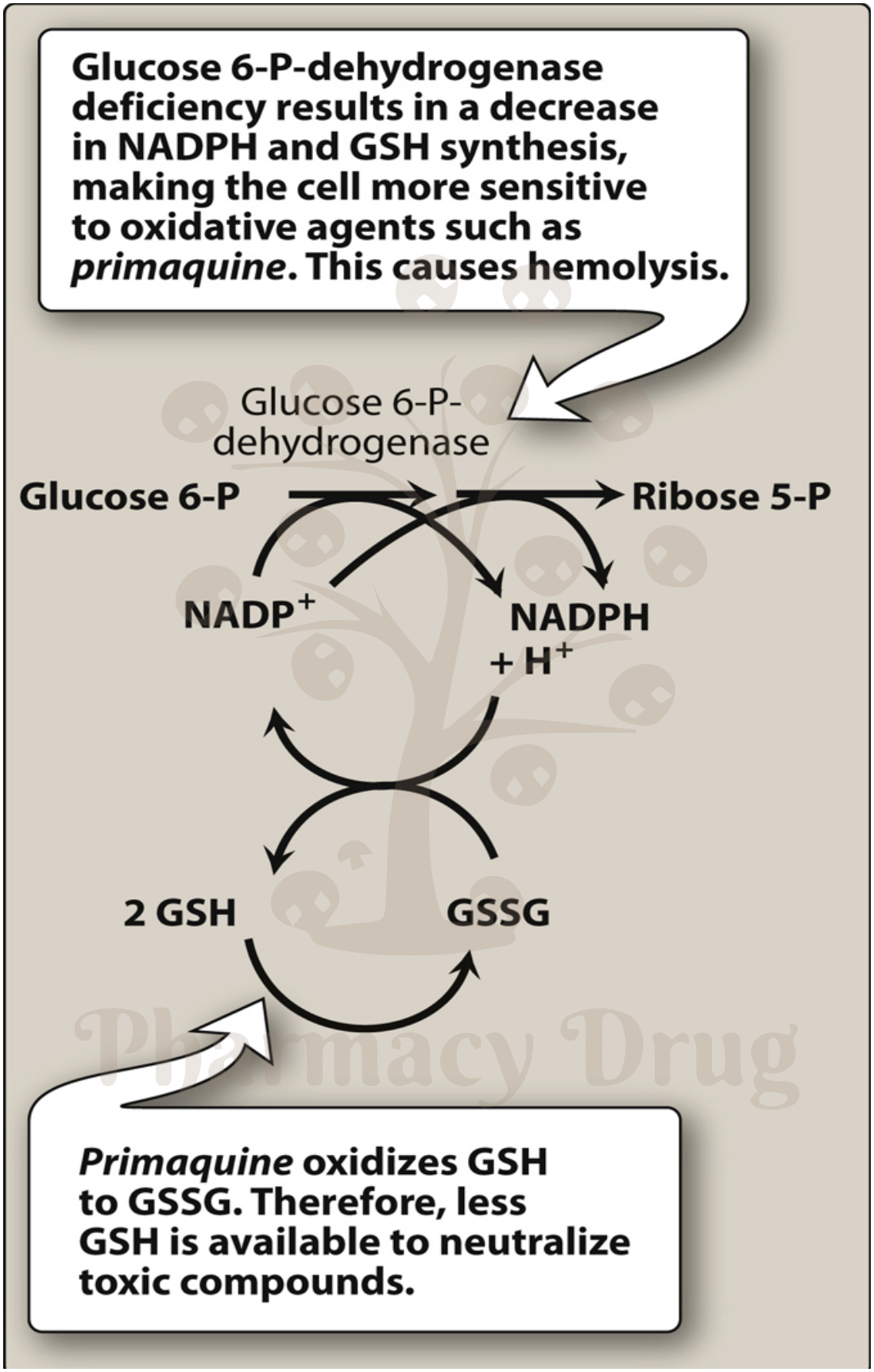

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Figure 35.6 Mechanism of *primaquine-induced* hemolytic anemia.GSH = reduced glutathione; GSSG = oxidized glutathione; $NADP^+$ = nicotinamide adenine dinucleotide phosphate; NADPH = reduced nicotinamide adenine dinucleotide phosphate.

B. Tafenoquine

Tafenoquine [ta-FEN-oh-kwin], a long-acting 8-aminoquinoline, is an oral antimalarial drug that primarily eradicates initial exoerythrocytic (liver) forms of plasmodia and the hypnozoites of recurring malarias (P. vivax and P. ovale). It is not indicated for the treatment of acute malaria. *Tafenoquine* is used for treatment of the dormant liver stage (hypnozoite) in P. vivax or P. ovale infections to prevent relapse of malaria, and like *primaquine*, it should not be used as monotherapy for treatment. The drug is also indicated for prevention - (chemoprophylaxis) of malaria during travel to endemic regions. *Tafenoquine* has a longer half-life when compared to *primaquine*, which allows for weekly dosing for prophylaxis (following three daily doses as the loading dose), or a single dose if used for prevention of relapse. Common adverse reactions include dizziness, nausea, vomiting, and headache. When used for chemoprophylaxis, elevated liver enzymes, insomnia, depression, abnormal dreams, and anxiety may occur. *Tafenoquine* is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency.

C. Chloroquine

Chloroquine is a synthetic 4-aminoquinoline that had been the mainstay of antimalarial therapy for many years; however, the use is now limited due to P. falciparum resistance, which is seen in almost all malaria-endemic areas, except some parts of Central America. *Chloroquine* is less effective against P. vivax malaria. *Chloroquine* is used in the prophylaxis of malaria for travel to areas with known *chloroquine*-sensitive malaria. It is also effective in the treatment of extraintestinal amebiasis.

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1.Mechanism of action: Although the mechanism of action is not fully understood, the processes essential for the antimalarial action of *chloroquine* are outlined in Figure 35.7. After traversing the erythrocytic and plasmodial membranes, *chloroquine* (a diprotic weak base) is concentrated in the acidic food vacuole of the malarial parasite, primarily by ion trapping. In the food vacuole, the parasite digests the host cell's hemoglobin to obtain essential amino acids. However, this process also releases large amounts of soluble heme, which is toxic to the parasite. To protect itself, the parasite polymerizes the heme to hemozoin (a pigment), which is sequestered in the food vacuole. *Chloroquine* specifically binds to heme, preventing its polymerization to hemozoin. The increased pH and the accumulation of heme result in oxidative damage to the phospholipid membranes, leading to lysis of both the parasite and the red blood cell.

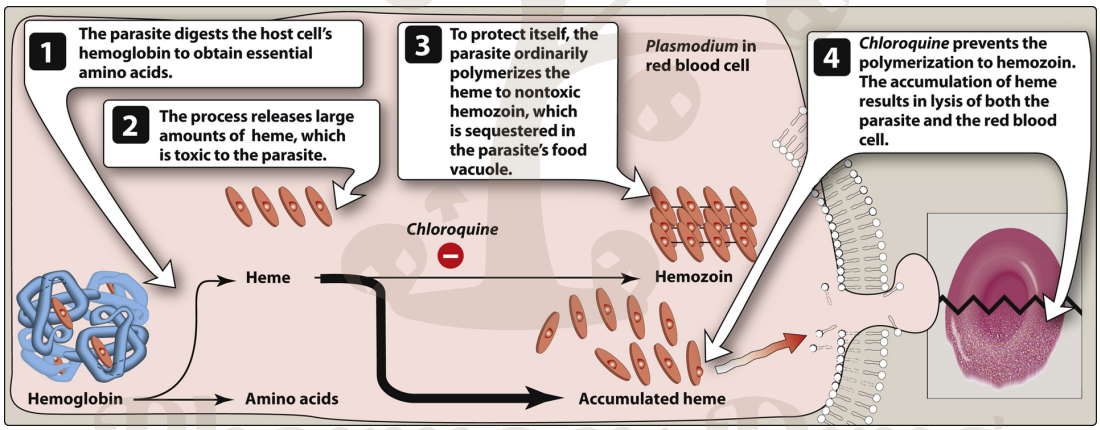

Figure 35.7 Action of *chloroquine* on the formation of hemozoin by *Plasmodium* species.

2.Pharmacokinetics: *Chloroquine* is rapidly and completely absorbed following oral administration. The drug has a very large volume of distribution and concentrates in erythrocytes, liver, spleen, kidney, lung, melanin-containing

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tissues, and leukocytes. It persists in erythrocytes. The drug also penetrates the central nervous system (CNS) and traverses the placenta. *Chloroquine* is dealkylated by the hepatic mixed-function oxidase system, and some metabolic products retain antimalarial activity. Both parent drug and metabolites are excreted predominantly in urine.

3.Adverse effects: Adverse effects are minimal at low prophylactic doses. At higher doses, gastrointestinal upset, pruritus, headaches, and blurred vision may occur (Figure 35.8). An ophthalmologic examination should be routinely performed during extended use due to potential retinal toxicity. Discoloration of the nail beds and mucous membranes may be seen on chronic administration. *Chloroquine* should be used cautiously in patients with hepatic dysfunction, severe gastrointestinal problems, or neurologic disorders. Patients with psoriasis or porphyria should not be treated with *chloroquine* because an acute attack may be provoked. *Chloroquine* can prolong the QT interval, and use of other drugs that also cause QT prolongation should be avoided if possible.

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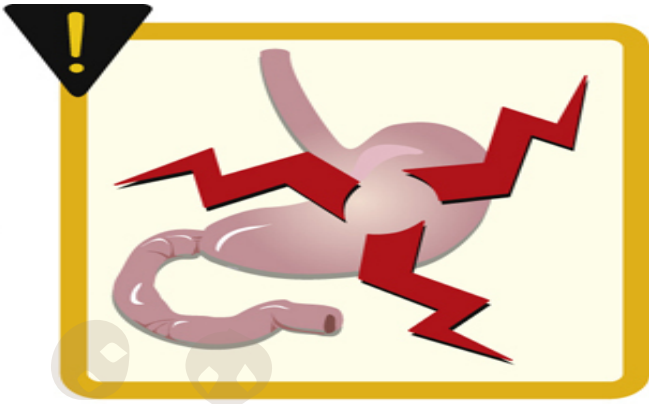
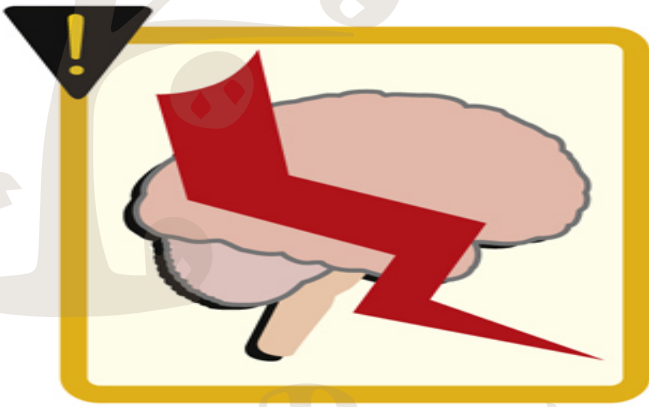
GI disturbance



Skin rash

Headache



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Blurred vision

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Figure 35.8 Some adverse effects commonly associated with *chloroquine*.GI = gastrointestinal.

D. Atovaquone–proguanil

The combination of *atovaquone–proguanil* [a-TOE-va-kwone pro-GWA-nil] is effective for *chloroquine*-resistant strains of P. falciparum, and it is used in the prevention and treatment of malaria for travelers from outside malaria-endemic areas. *Atovaquone–proguanil* is not routinely used in endemic areas due to propensity for emergence of high-level resistance. *Atovaquone* is a hydroxynaphthoquinone that inhibits mitochondrial processes including electron transport, as well as ATP and pyrimidine biosynthesis. Cycloguanil, the active triazine metabolite of *proguanil*, inhibits plasmodial dihydrofolate reductase, thereby preventing DNA synthesis. *Atovaquone* may also be used in the treatment of Babesia sp. and Pneumocystis jirovecii. *Proguanil* is metabolized via CYP2C19, an isoenzyme that is known to exhibit a genetic polymorphism, resulting in poor metabolism to the active metabolite cycloguanil in some patients. The combination should be taken with food or milk to enhance absorption. Common adverse effects include nausea, vomiting, abdominal pain, headache, diarrhea, anorexia, and dizziness.

E. Mefloquine

Mefloquine [MEF-lo-kwin] is a 4-methanolquinoline, structurally related to *quinine*, which is an effective agent for prophylaxis from all plasmodia. The drug may also be used for treatment of malaria due to P. vivax in combination with *primaquine* or *tafenoquine*, and for treatment of infections caused by multidrug-resistant forms of P. falciparum in combination with an *artemisinin* derivative. Its exact mechanism of action remains undetermined. Resistant strains have been identified, particularly in Southeast Asia. *Mefloquine* is well absorbed after oral administration, widely distributed to tissues, and concentrates in erythrocytes. It has a

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long half-life (20 days) because of enterohepatic recirculation and its concentration in various tissues. The drug undergoes partial metabolism in the liver and is primarily excreted via the bile into the feces. Adverse reactions at high doses range from nausea, vomiting, and dizziness to disorientation, hallucinations, and depression. Because of the potential for neuropsychiatric reactions, *mefloquine* is usually reserved for treatment of malaria when other agents cannot be used. Electrocardiogram abnormalities and cardiac arrest are possible if *mefloquine* is taken concurrently with *quinine* or *quinidine*.

F. Quinine

Quinine [KWYE-nine], an alkaloid originally isolated from the bark of the cinchona tree, interferes with heme polymerization, resulting in death of the erythrocytic form of the plasmodial parasite. It is reserved for treatment of severe infections and for *chloroquine*-resistant malarial strains. *Quinine* is usually administered in combination with *doxycycline*, *tetracycline*, or *clindamycin* (*primaquine or tafenoquine* are added for P. vivax infections to prevent relapse of malaria). Taken orally, *quinine* is well distributed throughout the body. The major adverse effect of *quinine* is cinchonism, a syndrome causing nausea, vomiting, tinnitus, and vertigo. These effects are reversible and are not reasons for suspending therapy. However, *quinine* treatment should be suspended if hemolytic anemia occurs.

G. Artemisinin

Artemisinin [ar-te-MIS-in-in] is derived from the sweet wormwood plant, which has been used in traditional Chinese medicine for many centuries. *Artemisinin* and its derivatives are recommended first-line agents for the treatment of multidrug-resistant P. falciparum malaria. The antimalarial action of *artemisinin* derivatives involves the production of free radicals resulting from cleavage of the drug's endoperoxide bridge by heme iron in the parasite food vacuole. Oral, rectal, intramuscular, and intravenous (IV) preparations are available, but the short half-lives preclude

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the use of these drugs for prophylaxis. *Artesunate* [ar-TEZ-oo-nate] is available in IV formulation and is a preferred treatment for severe malaria in areas where it is readily available. [Note: *Artesunate* should be administered with an antimalarial active against the hypnozoite liver stage (for example, *primaquine* or *tafenoquine*) in the treatment of severe P. vivax or P. ovale.] Following parenteral therapy with *artesunate*, an oral regimen should be continued for completion of antimalarial therapy. Addition of another antimalarial agent, or *artemisinin*-based combination therapy (ACT), is recommended to prevent the development of resistance. One orally available ACT includes a tablet with *artemether* coformulated with *lumefantrine* [AR-te-meth-er/loo-me-FAN-treen]. This agent is used for completion of therapy for severe malaria following parenteral therapy and also for the treatment of uncomplicated malaria. [Note: *Lumefantrine* is an antimalarial drug similar in action to *quinine* or *mefloquine*.] Adverse effects with *artesunate* include thrombocytopenia, hemolytic anemia, elevated liver enzymes, and hyperbilirubinemia. *Artemether–lumefantrine* has been associated with nausea, vomiting, and diarrhea. Hypersensitivity reactions and rash have occurred.

H. Pyrimethamine

Pyrimethamine [peer-i-METH-a-meen] inhibits plasmodial dihydrofolate reductase required for the synthesis of tetrahydrofolate (a cofactor needed for synthesis of nucleic acids). It acts as a blood schizonticide and a strong sporonticide when the mosquito ingests it with the blood of the human host. *Pyrimethamine* is not used alone for malaria; it is available as a fixed-dose combination with *sulfadoxine*, a sulfonamide antimicrobial. Resistance to this combination has developed, so it is usually administered with other agents, such as *artemisinin* derivatives. *Pyrimethamine* in combination with *sulfadiazine* is also used against Toxoplasma gondii. If megaloblastic anemia occurs with *pyrimethamine* treatment, it may be reversed with

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leucovorin. Figure 35.9 shows some therapeutic options in the treatment of malaria.

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TREATMENT OF MALARIA	
Uncomplicated malaria/P. falciparum or species not identified ***Chloroquine*-resistant or unknown resistance**	***Atovaquone-proguanil**** ***Artemether-lumefantrine*†** ***Mefloquine*** **or** ***Quinine*** **plus** ***Doxycycline, tetracycline,* or *clindamycin***
Uncomplicated malaria/P. falciparum or species not identified ***Chloroquine*-sensitive region**	***Chloroquine*** **Alternative: *Hydroxychloroquine***
Uncomplicated malaria/P. vivax or P. ovale	***Chloroquine* + *primaquine*** **or** ***Chloroquine* + *tafenoquine*** **Alternative: *hydroxychloroquine* + *primaquine***
Uncomplicated malaria/P. malariae or P. knowlesi	***Chloroquine*** **Alternatives: *Hydroxychloroquine*** ***Artemether/lumefantrine*** ***Atovaquone/proguanil***
Severe malaria	***Artesunate*†** **plus follow-on therapy with:** ***Artemether-lumefantrine* or** ***Atovaquone-proguanil* or** ***Quinine plus doxycycline* or** ***Mefloquine***
PREVENTION OF MALARIA	
***Chloroquine*-sensitive region**	***Chloroquine***
All other regions	***Atovaquone-proguanil*** ***Doxycycline*** ***Mefloquine***
During pregnancy	***Chloroquine* or *mefloquine***

Figure 35.9 Treatment and prevention of malaria. *Only for use in travelers outside malaria-endemic areas or added to combination regimen for alternative treatment regimens. † *Artemisinin*-based combination

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therapy is preferred according to World Health Organization. Infections with Plasmodium vivax or Plasmodium ovale require acute treatment and also treatment for prevention of relapse with *primaquine* or *tafenoquine*.

IV. CHEMOTHERAPY FOR BABESIOSIS

Babesiosis is a disease caused by intraerythrocytic protozoan parasites of the genus Babesia. Babesia is transmitted primarily during the bite from hard-bodied ticks with varying species present throughout the world. Babesia can also be transmitted through blood transfusions. The incidence of this protozoan infection has been rising in recent years, prompting increased screening of blood donors in endemic regions. Identification of acute babesiosis in a person with epidemiological risks for this infection can be done by microscopic evaluation of blood smears or by amplification of Babesia DNA using a polymerase chain reaction assay. Clinical manifestations of babesiosis include anorexia, fatigue, chills, sweats, headache, and fever. More severe complications can occur, including anemia and multiorgan failure leading to death. *Atovaquone* plus *azithromycin* as a combination for 7 to 10 days is recommended for acute babesiosis, while a combination of *clindamycin* plus *quinine* is an alternative treatment option. The mechanism of antiprotozoal action of *azithromycin* differs from the antibiotic mechanism. In Babesia, *azithromycin* targets the apicoplast, an organelle unique to protozoan parasites, which hosts important metabolic pathways.

V. CHEMOTHERAPY FOR TRYPANOSOMIASIS

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African trypanosomiasis (sleeping sickness) and American trypanosomiasis (Chagas disease) are two chronic and, eventually, fatal diseases caused by species of Trypanosoma. In African sleeping sickness, Trypanosoma brucei gambiense and Trypanosoma brucei rhodesiense initially live and grow in the blood. The parasite later invades the CNS, causing inflammation of the brain and spinal cord that produces the characteristic lethargy and, eventually, continuous sleep. Chagas disease is caused by Trypanosoma cruzi and is endemic in Central and South America. Antitrypanosomal drugs are outlined below.

Clinical Application 35.1: Treatment for Trypanosomiasis

Treatment choices are based on the causative trypanosome and the disease stage (Figure 35.10). The antiprotozoal agents for treatment of second stage caused by one of the Trypanosoma brucei species must cross the blood–brain barrier and tend to be more toxic and complex to administer than first-stage medicines. Encephalopathic syndrome from melarsoprol is a significant and sometimes fatal adverse effect; however, infection of the CNS with Trypanosoma brucei rhodesiense is often a fatal disease if left untreated.

POLE STAR

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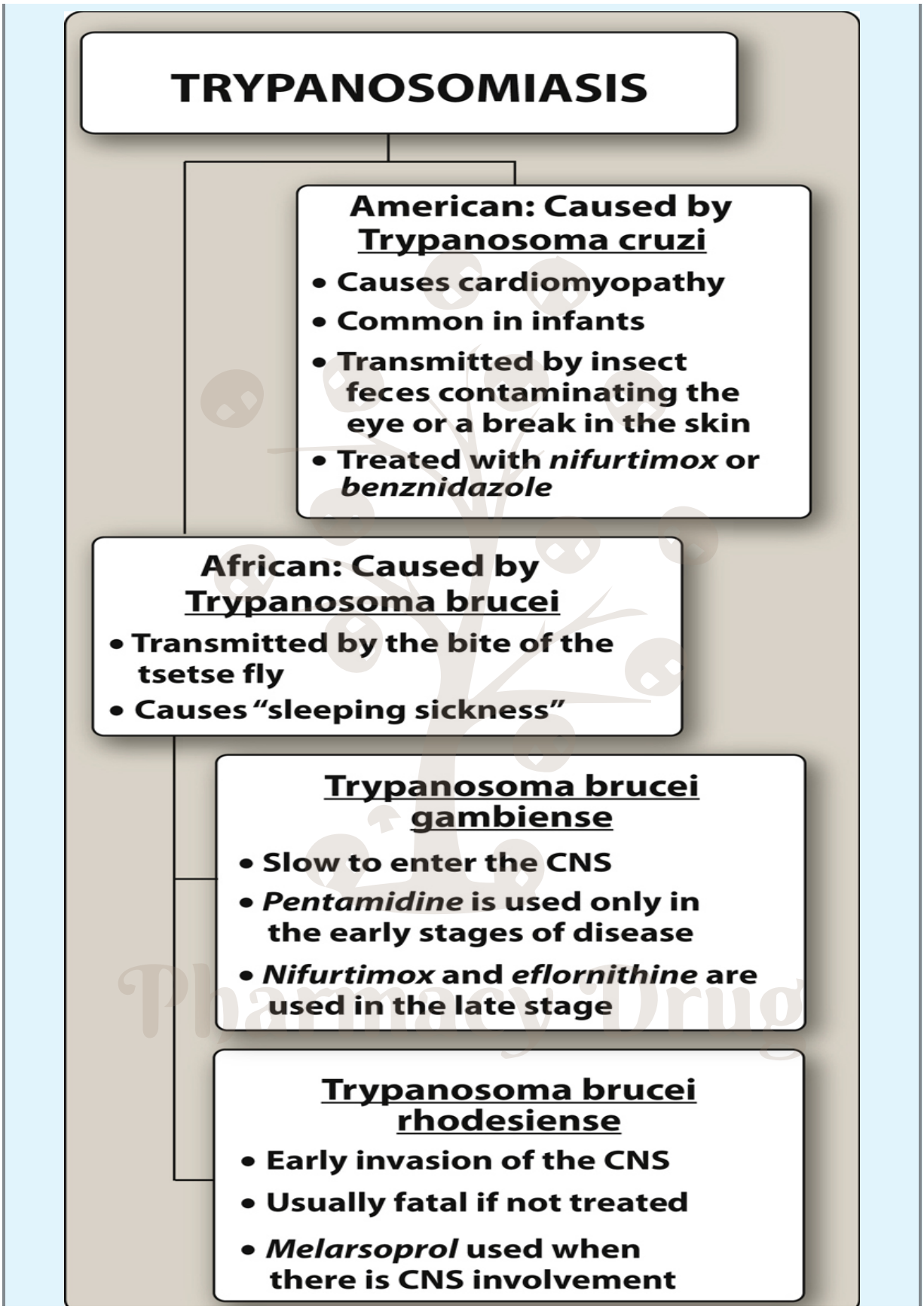

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Figure 35.10 Summary of trypanosomiasis.CNS = central nervous system.

A. Pentamidine

Pentamidine [pen-TAM-i-deen] is active against a variety of protozoal infections, including African trypanosomiasis due to T. brucei gambiense, for which it is first-line treatment for the early stages of disease (hemolymphatic stage without CNS involvement). *Pentamidine* is also an alternative for prophylaxis or treatment of infections caused by P. jirovecii. [Note: P. jirovecii is an atypical fungus that causes pneumonia in immunocompromised patients, such as those with human immunodeficiency virus infection. *Trimethoprim/sulfamethoxazole* is preferred in the treatment of P. jirovecii infections; however, *pentamidine* is an alternative in individuals who are allergic to sulfonamides.] *Pentamidine* is also an alternative drug for the treatment of leishmaniasis.

1. Mechanism of action: T. brucei concentrates *pentamidine* by an energy-dependent, high-affinity uptake system. [Note: Resistance is associated with inability to concentrate the drug.] Although its mechanism of action has not been defined, evidence exists that the drug interferes with parasite synthesis of ribonucleic acid, DNA, phospholipids, and proteins.

2. Pharmacokinetics: *Pentamidine* is administered intramuscularly or intravenously for the treatment of trypanosomiasis and pneumonia caused by *P. jirovecii.* [Note: For prophylaxis of P. jirovecii pneumonia, *pentamidine* is administered via nebulizer.] The drug distributes widely and is concentrated in the liver, kidney, adrenals, spleen, and lungs. Because it does not enter the CSF, it is ineffective against the late stages (CNS involvement) of trypanosomiasis. Metabolism

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of the drug has not been characterized, and it is excreted very slowly in the urine.

3.Adverse effects: Serious renal dysfunction may occur, which is reversible on discontinuation. Other adverse reactions include hyperkalemia, hypotension, pancreatitis, ventricular arrhythmias, and hyperglycemia. Plasma glucose should be monitored, as life-threatening hypoglycemia can occur.

B. Suramin

Suramin [SOO-ra-min] is used primarily in the early stage (without CNS involvement) of African trypanosomiasis due to T. brucei rhodesiense. It is very reactive and inhibits many enzymes, especially those involved in energy metabolism, which appears to be the mechanism correlated with trypanocidal activity. *Suramin* must be injected intravenously. It binds to plasma proteins and does not penetrate the blood–brain barrier well. It has a long elimination half-life (greater than 40 days) and is mainly excreted unchanged in the urine. Although infrequent, adverse reactions include nausea and vomiting, shock and loss of consciousness, acute urticaria, blepharitis, and neurologic problems, such as paresthesia, photophobia, and hyperesthesia of the hands and feet. Renal insufficiency may occur but tends to resolve with discontinuation of treatment. Acute hypersensitivity reactions may occur, and a test dose should be given prior to drug administration.

C. Melarsoprol

Melarsoprol [mel-AR-so-prol], a trivalent arsenical compound, is the only medication available for treatment of late stages of African trypanosome infections (CNS involvement) due to T. brucei rhodesiense. The drug reacts with sulfhydryl groups of various substances, including pyruvate kinase enzymes in both the organism and host. Some resistance has been noted, and it may be due to decreased transporter uptake of the drug. *Melarsoprol* is administered by slow IV injection and can be very

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irritating to the surrounding tissue. Adequate trypanocidal concentrations appear in the CSF, making *melarsoprol* the agent of choice in the treatment of *T. brucei rhodesiense*, which rapidly invades the CNS. The host readily oxidizes *melarsoprol* to a relatively nontoxic, pentavalent arsenic compound. The drug has a very short half-life and is rapidly excreted in urine. The use of *melarsoprol* is limited by CNS toxicity, including reactive encephalopathy, which can be fatal in 10% of cases. Concurrent administration of corticosteroids may reduce the risk of encephalopathy. Other adverse effects include peripheral neuropathy, hypertension, hepatotoxicity, and albuminuria. Hypersensitivity reactions may also occur, and febrile reactions may follow injection. Hemolytic anemia has been seen in patients with glucose-6-phosphate dehydrogenase deficiency.

D. Eflornithine

Eflornithine [ee-FLOOR-nih-theen] is an irreversible inhibitor of ornithine decarboxylase. Inhibition of this enzyme halts the production of polyamines in the parasite, thereby leading to cessation of cell division. The IV formulation of *eflornithine* used in combination with *nifurtimox* is a first-line treatment for late-stage African trypanosomiasis caused by T. brucei gambiense. [Note: Topical *eflornithine* is used as a treatment for unwanted facial hair in women.] The short half-life of *eflornithine* necessitates frequent IV administration, making the treatment regimen difficult to follow. Adverse reactions with *eflornithine* include anemia, thrombocytopenia, seizures, and temporary hearing loss.

E. Nifurtimox

Nifurtimox [nye-FER-tim-oks] is used for the treatment of late-stage T. brucei gambiense in combination with *eflornithine.* It is also used in the treatment of T. cruzi infections (Chagas disease), although treatment of the chronic stage of such infections has led to variable results. Being a nitroaromatic compound, *nifurtimox* undergoes reduction and eventually generates intracellular oxygen radicals, such as superoxide radicals and hydrogen

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peroxide (Figure 35.11). These highly reactive radicals are toxic to T. cruzi. *Nifurtimox* is administered orally. It is extensively metabolized, and the metabolites are excreted mainly in the urine. Adverse effects are common following chronic administration, particularly among the elderly. Major toxicities include hypersensitivity reactions (anaphylaxis, dermatitis) and gastrointestinal problems that may be severe enough to cause weight loss. Peripheral neuropathy is relatively common, and headache and dizziness may also occur.

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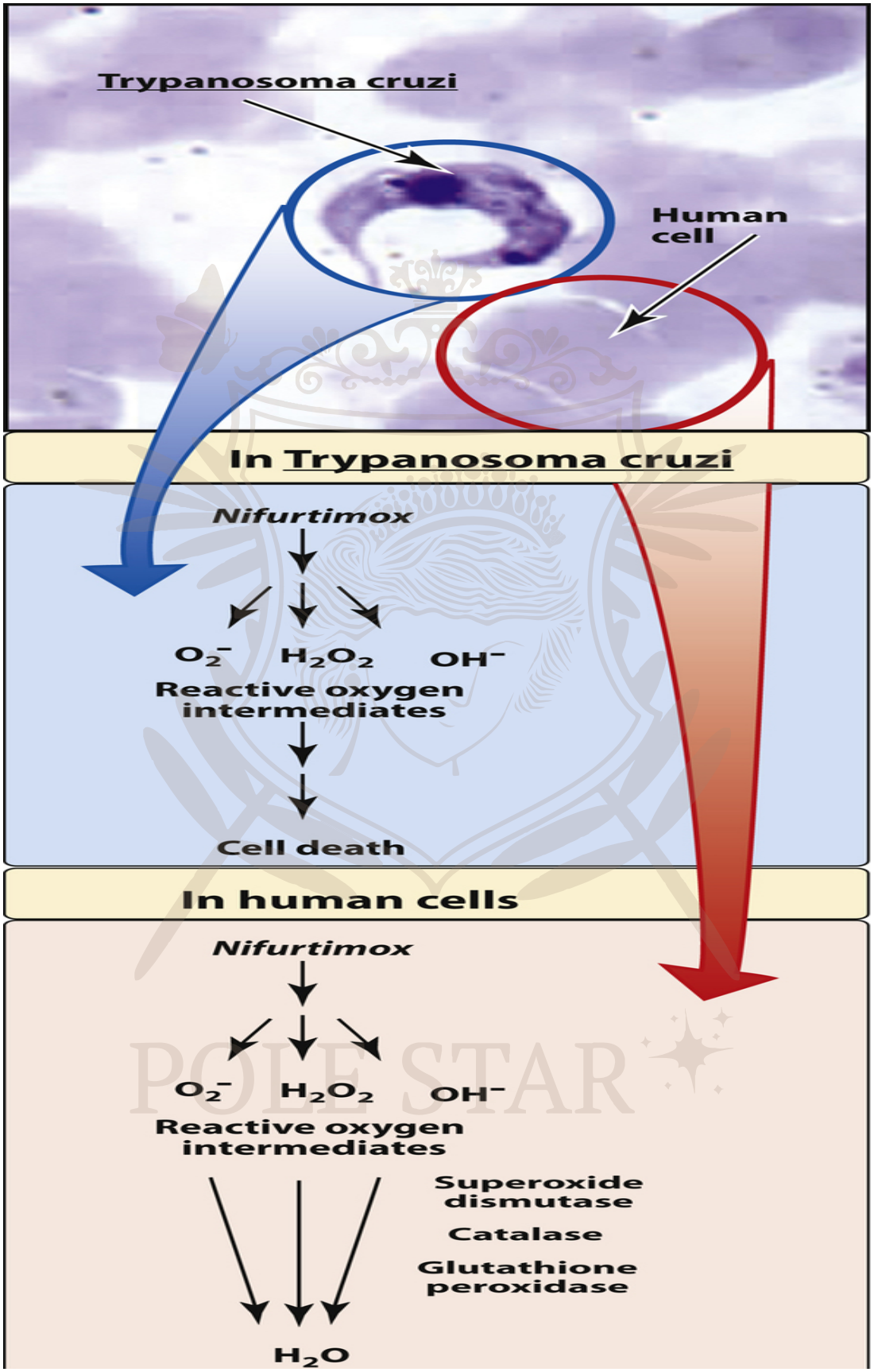
Trypanosoma cruzi
Human cell
In Trypanosoma cruzi
Nifurtimox
O_2^- H_2O_2 OH^-
Reactive oxygen intermediates
Cell death
In human cells
Nifurtimox
O_2^- H_2O_2 OH^-
Reactive oxygen intermediates
Superoxide dismutase
Catalase
Glutathione peroxidase
H_2O

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Figure 35.11 Generation of toxic intermediates by *nifurtimox*.

F. Benznidazole

Benznidazole [benz-NI-da-zole] is a nitroimidazole derivative with a mechanism of action similar to *nifurtimox.* It tends to be better tolerated than *nifurtimox* for the treatment of Chagas disease. Adverse effects include dermatitis, peripheral neuropathy, insomnia, and anorexia. Both *benznidazole* and *nifurtimox* should be avoided in pregnancy due to potential fetal harm.

VI. CHEMOTHERAPY FOR LEISHMANIASIS

Leishmaniasis is a protozoal infection caused by various species of the genus Leishmania. There are three manifestations of leishmaniasis: cutaneous, mucocutaneous, and visceral. [Note: In the visceral type (liver and spleen), the parasite is in the bloodstream and if untreated is fatal.] Leishmaniasis is transmitted by the bite of infected sand flies. For visceral leishmaniasis, parenteral treatments may include *amphotericin B* (see Chapter 33) and pentavalent antimonials, such as *sodium stibogluconate* or *meglumine antimoniate* with *pentamidine* and *paromomycin* as alternative agents. *Miltefosine* is an orally active agent for visceral leishmaniasis. The choice of agent depends on the species of Leishmania, host factors, and resistance patterns noted in area of the world where the infection is acquired.

A. Sodium stibogluconate

The pentavalent antimonial *sodium stibogluconate* [stib-o-GLOO-koe-nate] is a prodrug which is reduced to the active trivalent antimonial compound. The exact mechanism of action has not been determined. Because it is not absorbed after oral

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administration, *sodium stibogluconate* must be administered parenterally, and it is distributed in the extravascular compartment. Metabolism is minimal, and the drug is excreted in urine. Adverse effects include injection site pain, pancreatitis, elevated liver enzymes, arthralgias, myalgias, gastrointestinal upset, and cardiac arrhythmias. Resistance to the pentavalent antimonials has developed.

B. Miltefosine

Miltefosine [mil-te-FOE-zeen] is an orally active drug for visceral leishmaniasis and can also treat cutaneous and mucocutaneous forms of the disease. The precise mechanism of action is not known, but *miltefosine* appears to interfere with phospholipids and sterols in the parasitic cell membrane to induce apoptosis. Nausea and vomiting are common adverse reactions. The drug is teratogenic and should be avoided in pregnancy.

VII. CHEMOTHERAPY FOR TOXOPLASMOSIS

One of the most common infections in humans is caused by the protozoan T. gondii, which is transmitted to humans when they consume raw, inadequately cooked infected meat, water contaminated with sporulated oocysts, or accidentally ingest oocysts from cat feces. An infected pregnant woman can transmit T. gondii to her fetus. Immunocompromised patients can present with severe disseminated disease. Current treatments for toxoplasmosis target the tachyzoite stage of the protozoan, with *pyrimethamine* being the most effective agent as part of a combination therapy regimen. The treatment of choice for this condition is a combination of *sulfadiazine* and *pyrimethamine. Leucovorin* is commonly administered to protect against folate deficiency. [Note: At the first appearance of a rash, *pyrimethamine* should be discontinued because hypersensitivity to this drug can be severe.] *Pyrimethamine* with *clindamycin* or the

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combination of *trimethoprim* and *sulfamethoxazole* are alternative treatments. *Trimethoprim/sulfamethoxazole* is used for prophylaxis against toxoplasmosis (as well as P. jirovecii) in immunocompromised patients.

VIII. CHEMOTHERAPY FOR GIARDIASIS

G. lamblia is the most commonly diagnosed intestinal parasite in the United States. It has two life cycle stages: the binucleate trophozoite with four flagella and the drug-resistant, four-nucleate cyst (Figure 35.12). Infection usually occurs from ingestion of fecally contaminated drinking water or food. The trophozoites exist in the small intestine and divide by binary fission. Occasionally, cysts are formed that pass in stools. Although some infections are asymptomatic, severe diarrhea can occur, which can be very serious in immunocompromised patients. The treatment of choice is a single dose of oral *tinidazole.* Oral *metronidazole* for 5 days is an alternative therapy. *Nitazoxanide* [nye-ta-ZOX-a-nide], a nitrothiazole derivative, is also approved for the treatment of giardiasis. [Note: *Nitazoxanide* may also be used for cryptosporidiosis (a diarrheal illness most commonly seen in immunocompromised patients) caused by the parasite Cryptosporidium parvum.] For giardiasis, *nitazoxanide* is administered as a 3-day course of oral therapy. The anthelmintic drug *albendazole* may also be efficacious for giardiasis, and *paromomycin* is sometimes used for treatment of giardiasis in pregnant patients.

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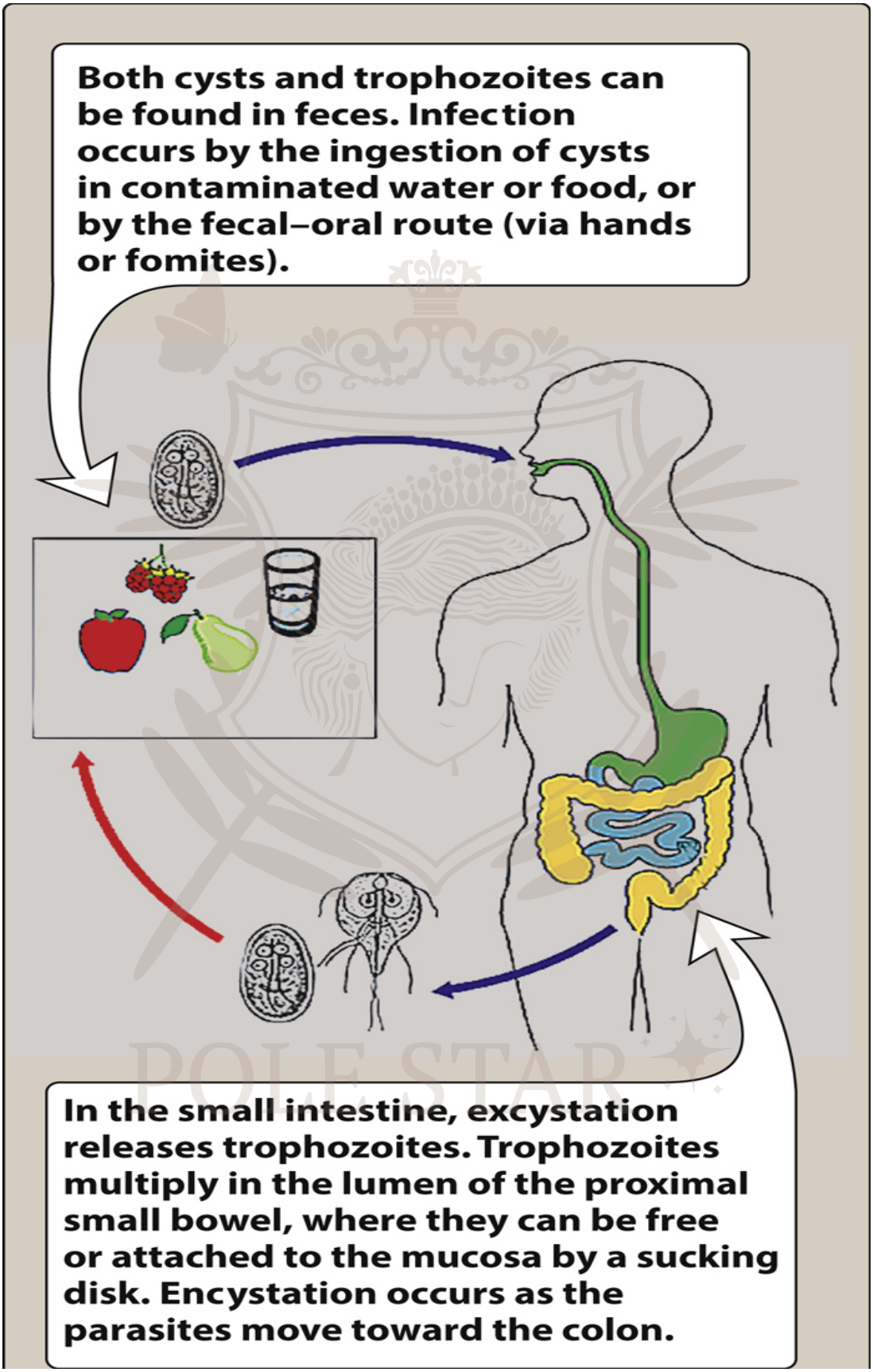
Both cysts and trophozoites can be found in feces. Infection occurs by the ingestion of cysts in contaminated water or food, or by the fecal–oral route (via hands or fomites).
In the small intestine, excystation releases trophozoites. Trophozoites multiply in the lumen of the proximal small bowel, where they can be free or attached to the mucosa by a sucking disk. Encystation occurs as the parasites move toward the colon.

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Figure 35.12 Life cycle of *Giardia lamblia*.

Chapter Summary

- Pregnancy status is an important treatment consideration when treating parasitic infections because most antiprotozoal agents have not been proven safe for use in pregnant patients.
- *Primaquine* and *tafenoquine* are the only antiprotozoal agents with activity against the dormant (hypnozoite) stage in P. vivax infections and are necessary additions to therapy to achieve a cure and prevent relapse.
- Chemoprophylaxis for malaria in travelers should consider *Plasmodium* resistance in the destination countries. *Chloroquine* had been the mainstay of antimalarial therapy and chemoprophylaxis for many years; however, the use is now limited due to P. falciparum resistance, which is seen in almost all malaria-endemic areas, except some parts of Central America.
- Many of the antiprotozoal agents cause serious toxic effects in the host, and treatment is often determined by the stage or severity of the disease to limit the use of unnecessary toxic medications.

STUDY QUESTIONS

Choose the ONE best answer.

35.1 After the acute infection, which of the following medications is given to treat the asymptomatic colonization state of E. histolytica?

A. Chloroquine
B. Iodoquinol
C. Metronidazole
D. Primaquine

Correct answer = B. Iodoquinol, diloxanide furoate, and paromomycin are luminal amebicides that are usually administered with mixed or systemic amebicides to treat the asymptomatic colonization state. Chloroquine is a

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systemic amebicide and an antimalarial. Metronidazole is a mixed amebicide. Primaquine is an antimalarial.

35.2 A 35-year-old man is being treated for amebiasis. After consumption of an alcoholic beverage, he has a severe reaction that includes nausea, vomiting, and flushing. Which of the following agents most likely contributed to his reaction to alcohol?

A. Chloroquine
B. Metronidazole
C. Primaquine
D. Pyrimethamine

Correct answer = B. Nitroimidazole agents, such as metronidazole and tinidazole, can cause a disulfiram-like reaction in patients who ingest alcohol during therapy. Symptoms include nausea, vomiting, flushing, headache, and general discomfort. Alcohol should be avoided with these agents. The other drugs are not known to cause similar symptoms with ingestion of alcohol.

35.3 Which of the following statements regarding paromomycin is correct?

A. Paromomycin is only effective against the luminal forms of E. histolytica.
B. The principle adverse effects are optic neuritis and peripheral neuropathy.
C. Paromomycin is considered a nitroimidazole.
D. If taken with alcohol, a disulfiram-like reaction may occur.

POLE STAR

Correct answer = A. Paromomycin is an aminoglycoside antibiotic, known as a luminal amebicide. It is only effective against the luminal forms of E. histolytica because it is not significantly absorbed from the gastrointestinal tract. The principle adverse effects are gastrointestinal distress and diarrhea. The nitroimidazoles should be avoided with alcohol consumption due to the risk of a disulfiram-like reaction.

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35.4 A 32-year-old pregnant woman is traveling abroad to a malaria-endemic country with known chloroquine resistance. Which of the following prophylactic regimens is most appropriate?

A. Doxycycline
B. Mefloquine
C. Primaquine
D. Artemether–lumefantrine

Correct answer = B. Mefloquine is one of the preferred regimens for malaria prophylaxis in a pregnant woman. Doxycycline and primaquine are not recommended for use in pregnancy. Artemether–lumefantrine is only recommended for the treatment, not prophylaxis, of malaria.

35.5 Which of the following treatment options is most appropriate to add to artemether–lumefantrine for prevention of relapse in a patient with uncomplicated malaria due to P. vivax?

A. Tafenoquine
B. Doxycycline
C. Miltefosine
D. Mefloquine

Correct answer = A. Tafenoquine is an antimalarial medication that has activity against the dormant hypnozoite liver stage of P. vivax infections and it is indicated to prevent relapses. Doxycycline and mefloquine are not active against the hypnozoite liver stage of P. vivax infections. Miltefosine is used for leishmaniasis.

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35.6 A diagnosis of babesiosis is made in a 23-year-old man. Which of the following is a preferred therapy for this patient?

A. Atovaquone plus azithromycin
B. Clindamycin
C. Paromomycin plus metronidazole
D. Quinine

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Correct answer = A. Atovaquone plus azithromycin as a combination is the preferred therapy for acute babesiosis. Clindamycin is an option to treat babesiosis; however, it must be combined with quinine. Paromomycin plus metronidazole is a recommended combination therapy for amebic dysentery with systemic symptoms. Quinine is used in the treatment of malaria.

35.7 Which of the following agents is the only medication to treat late stages of trypanosomal infections due to T. brucei rhodesiense?

A. Artemether–lumefantrine
B. Melarsoprol
C. Nitazoxanide
D. Tinidazole

Correct answer = B. Melarsoprol is the only agent available for the treatment of late-stage trypanosomal infections due to T. brucei rhodesiense. All the other drugs are used for other indications; artemether–lumefantrine is used for the treatment of malaria, nitazoxanide is used for the treatment of giardiasis or cryptosporidiosis, and tinidazole is effective for amebiasis or giardiasis.

35.8 A 3-year-old boy is diagnosed with Chagas disease. Which of the following agents is most appropriate for treatment of this patient?

A. Benznidazole
B. Sodium stibogluconate
C. Pentamidine
D. Suramin

POLE STAR

Correct answer = A. Benznidazole is used for treatment of Chagas disease (*T. cruzi*). Sodium stibogluconate is used for the treatment of visceral leishmaniasis. Both pentamidine and suramin are used primarily for the treatment of African trypanosomiasis.

35.9 Which of the following agents is available as an oral therapy for the treatment of visceral leishmaniasis?

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A. Artemether–lumefantrine
B. Miltefosine
C. Nitazoxanide
D. Tinidazole

Correct answer = B. Miltefosine is the only oral agent available for the treatment of visceral leishmaniasis. All the other drugs are orally administered, but artemether–lumefantrine is used for the treatment of malaria, nitazoxanide is used for the treatment of giardiasis or cryptosporidiosis, and tinidazole is effective for amebiasis or giardiasis.

35.10 A 42-year-old man returned from a camping trip and is diagnosed with *Giardia lamblia.* Which of the following medications would be considered the treatment of choice?

A. Chloroquine
B. Nifurtimox
C. Paromomycin
D. Tinidazole

Correct answer = D. Tinidazole is used for the treatment of amebiasis and giardiasis. Chloroquine is used for the treatment of malaria and extraintestinal amebiasis. Nifurtimox is indicated for the treatment of American trypanosomiasis (Chagas disease) caused by T. cruzi and also for the treatment of T. brucei gambiense. Paromomycin is used for the treatment of luminal forms of E. histolytica.

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36

Anthelmintic Drugs

Kelli A. Kronsberg, Jonathan C. Cho, Marylee V. Worley

I. OVERVIEW

Nematodes, trematodes, and cestodes are the three major groups of helminths (worms) that infect humans. Anthelmintic drugs (Figure 36.1) are aimed at metabolic targets that are present in the parasite but either are absent from or have different characteristics than those of the host. Figure 36.2 illustrates the high incidence of common helmintic infections worldwide. Most anthelmintics target eliminating the organisms from the host, as well as controlling spread of infections.

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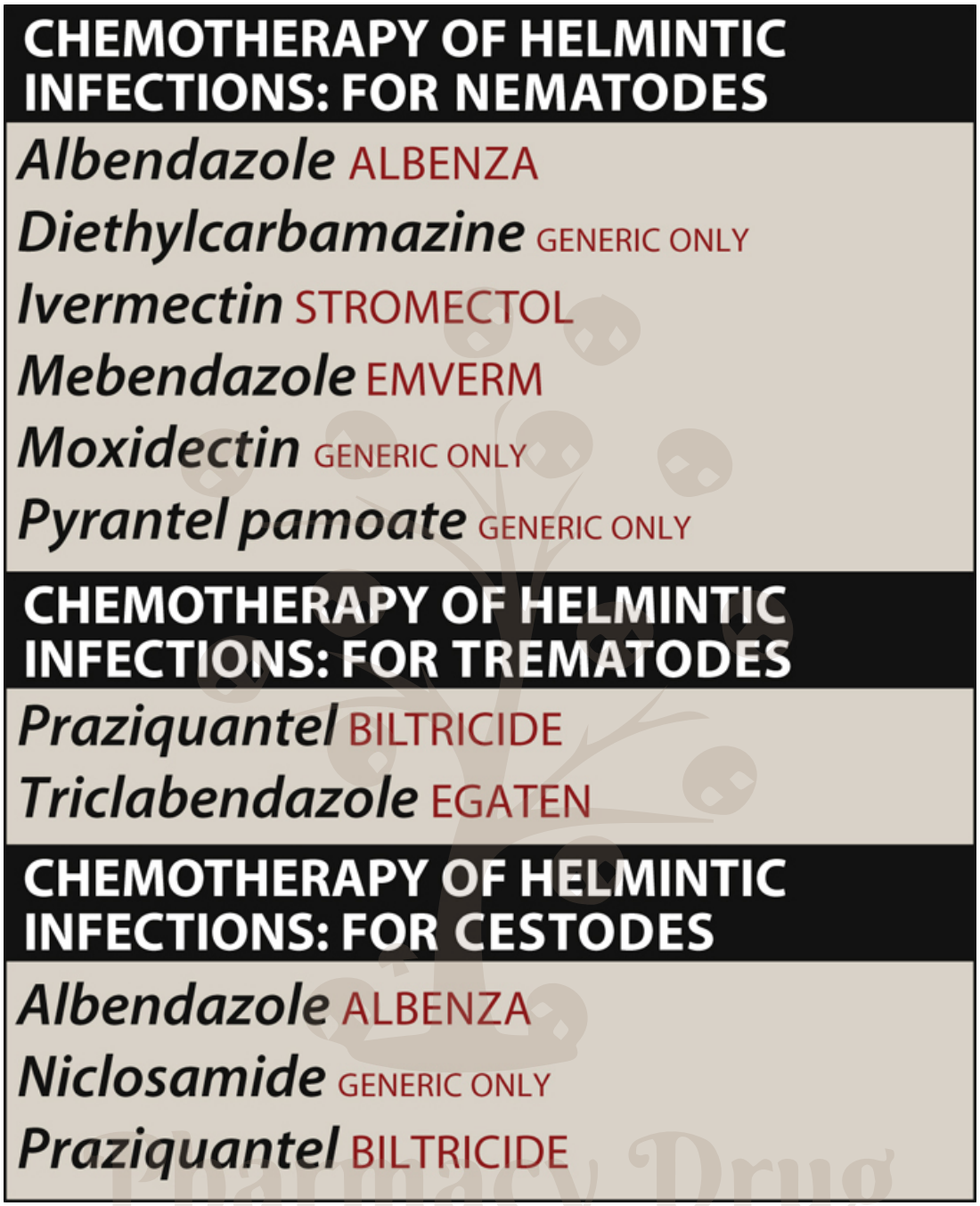

Figure 36.1 Summary of anthelmintic agents.

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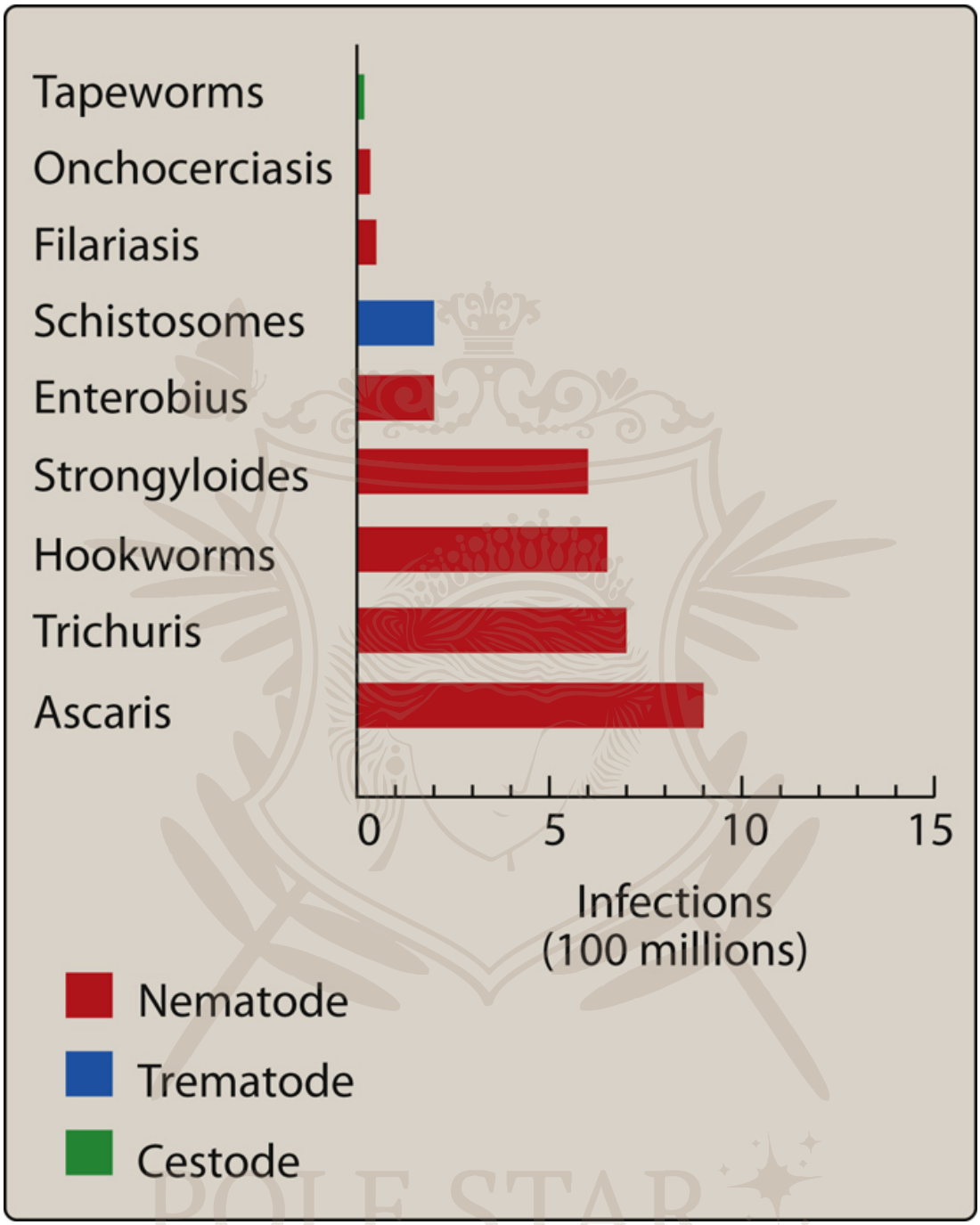

Figure 36.2 Global incidence estimates of common helminth infections.

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II. DRUGS FOR THE TREATMENT OF NEMATODES

Nematodes are elongated roundworms that possess a complete digestive system. They cause infections of the intestine as well as the blood and tissues.

A. Mebendazole

Mebendazole [me-BEN-da-zole], a synthetic benzimidazole compound, is a first-line agent for the treatment of infections caused by whipworms (Trichuris trichiura), pinworms (Enterobius vermicularis), hookworms (Necator americanus and Ancylostoma duodenale), and roundworms (Ascaris lumbricoides). *Mebendazole* and benzimidazoles as a class act by binding to parasite β-tubulin and inhibiting microtubule polymerization in the parasite. Affected parasites are expelled in the feces. Common adverse effects include abdominal pain and diarrhea. Rare but serious adverse effects include convulsions in pediatric patients less than 1 year of age and an increased risk of Stevens–Johnson syndrome or toxic epidermal necrolysis when *mebendazole* is administered in combination with *metronidazole. Mebendazole* should not be used in pregnant women. [Note: Many anthelmintics should be avoided in pregnancy (Figure 36.3); however, in mass prevention or treatment programs, certain agents (for example, *mebendazole* or *albendazole*) may be used in the second or third trimester.]

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Figure 36.3 Anthelmintic drugs that should be avoided in pregnancy.

B. Pyrantel pamoate

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Pyrantel pamoate [pi-RAN-tel PAM-oh-ate] is also effective in the treatment of infections caused by pinworms and hookworms (Figure 36.4). *Pyrantel pamoate* is poorly absorbed after oral administration and is only effective against intestinal infections. It acts as a depolarizing neuromuscular blocking agent, causing release of acetylcholine and inhibition of cholinesterase, leading to paralysis of the worm and subsequent expulsion. As this mechanism does not affect pinworm eggs, a second dose must be administered to fully eradicate the infection. Adverse effects are mild and include nausea, vomiting, and diarrhea.

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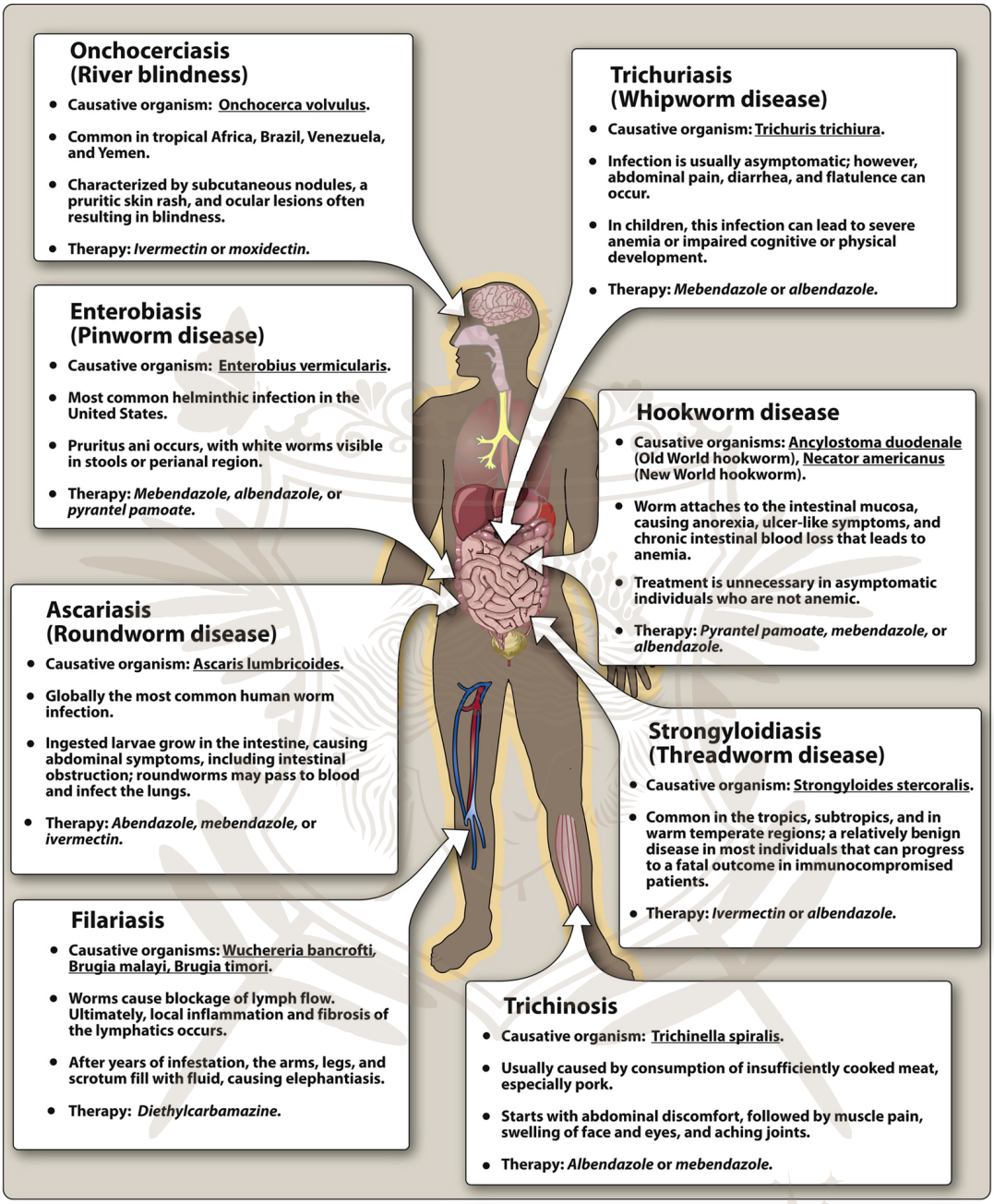

Figure 36.4 Characteristics of and therapy for commonly encountered nematode infections.

C. Ivermectin

Ivermectin [eye-ver-MEK-tin] is the drug of choice for the treatment of cutaneous larva migrans, strongyloidiasis, and

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onchocerciasis (river blindness, although not curative due to lack of activity in adult worms). [Note: *Ivermectin* is also useful in the treatment of scabies and a topical formulation is used to treat pediculosis capitis (head lice).] *Ivermectin* targets the glutamate-gated chloride channel receptors. Chloride influx is enhanced, and hyperpolarization occurs, resulting in paralysis and death of the worm. The drug is given orally and does not readily cross the blood–brain barrier. *Ivermectin* should not be used in pregnancy (see Figure 36.3). The killing of the microfilaria in onchocerciasis can result in a dangerous Mazzotti reaction (fever, headache, dizziness, somnolence, and hypotension). The severity of this reaction is related to parasite load. Antihistamines or steroids may be given to ameliorate the symptoms.

Clinical Application 36.1: Hyperinfection Syndrome and Disseminated Strongyloidiasis

Hyperinfection syndrome and disseminated strongyloidiasis are typically seen in immunocompromised patients, such as those with human T-cell lymphotropic virus 1 (HTLV-1), or those receiving immunosuppressant medications, such as chronic corticosteroid therapy. Mortality rates for this disorder are up to 90% without treatment. While acute or chronic strongyloidiasis is treated for 1 to 2 days, patients with hyperinfection syndrome and disseminated strongyloidiasis are treated with *ivermectin* daily until stool and/or sputum examinations are negative for 2 weeks.

D. Moxidectin

Moxidectin [mox-i-DEK-tin] is an alternative to *ivermectin* for the treatment of onchocerciasis. This agent has a similar mechanism of action, and it also lacks activity against adult worms. The safety of *moxidectin* in pregnancy has not been established. Death of microfilaria in onchocerciasis following use of this agent can result in the dangerous Mazzotti reaction.

E. Diethylcarbamazine

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Diethylcarbamazine [dye-eth-il-kar-BAM-a-zeen] is the drug of choice for filariasis caused by infection with Wuchereria bancrofti, Brugia malayi, or Brugia timori. It kills the microfilariae and has activity against adult worms. [Note: In countries where filariasis is endemic, various regimens of antifilarial drugs (*diethylcarbamazine*, *albendazole*, and *ivermectin*) may be used annually as preventive chemotherapy.] *Diethylcarbamazine* is rapidly absorbed following oral administration with meals and is excreted mainly in the urine. Adverse effects may include fever, nausea, vomiting, arthralgia, and headache. [Note: *Diethylcarbamazine* is contraindicated in patients coinfected with onchocerciasis, since it can accelerate blindness and cause severe Mazzotti reactions.]

III. DRUGS FOR THE TREATMENT OF TREMATODES

The trematodes (flukes) are leaf-shaped flatworms that are generally characterized by the tissues they infect (for example, liver, lung, intestinal, or blood; Figure 36.5).

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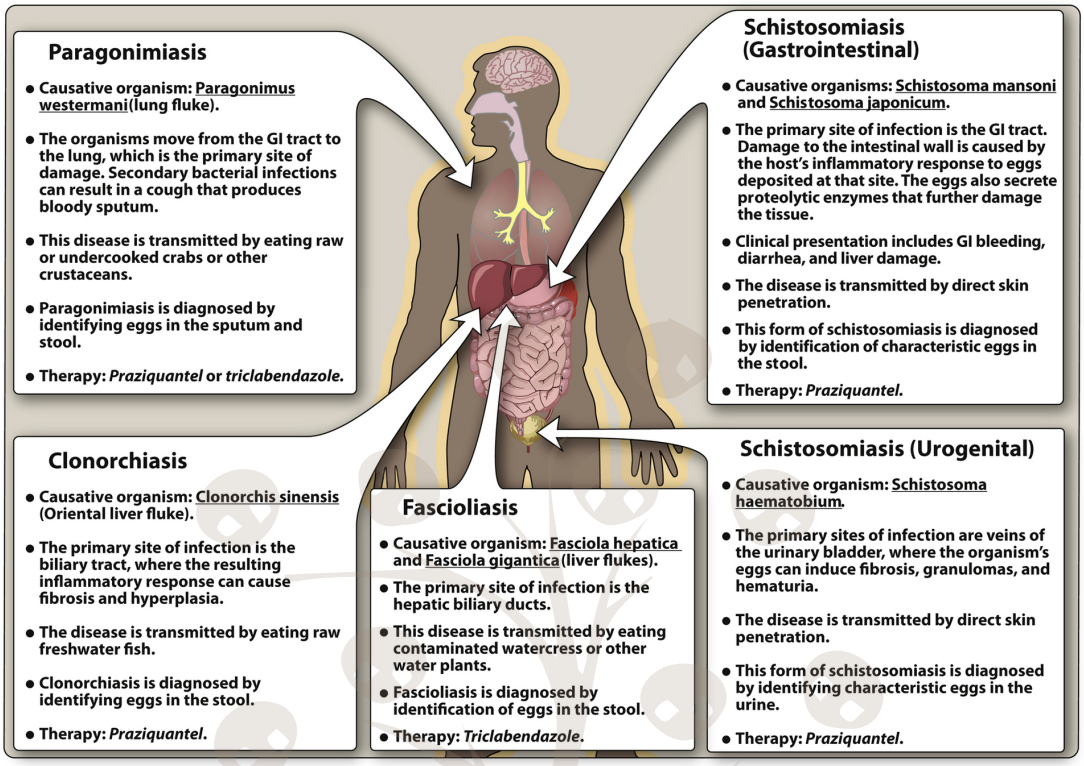

Figure 36.5 Characteristics of and therapy for commonly encountered trematode infections.GI = gastrointestinal.

A. Praziquantel

Praziquantel [pray-zi-KWON-tel] is an agent of choice for the treatment of all forms of schistosomiasis, other trematode infections (with the exception of fascioliasis), and cestode infections such as taeniasis. *Praziquantel* causes contracture and paralysis of parasites by increasing the permeability of the cell membrane to calcium. It is rapidly absorbed after oral administration and should be taken with food. The drug is extensively metabolized, and the inactive metabolites are excreted primarily in the urine. Common adverse effects include dizziness, malaise, and headache as well as gastrointestinal upset. Strong CYP3A4 inducers, such as *phenytoin*, *rifampin*, and *carbamazepine*, increase the metabolism of *praziquantel* and reduce its efficacy. Concurrent use of these drugs with

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praziquantel is contraindicated. *Praziquantel* is contraindicated for the treatment of ocular cysticercosis, because destruction of the organism in the eye may cause irreversible damage.

B. Triclabendazole

Triclabendazole [try-KLUH-bend-uh-zole] is a benzimidazole derivative that is for the treatment of fascioliasis (liver flukes) caused by Fasciola hepatica and Fasciola gigantica. It is thought to inhibit tubulin function as well as protein and enzyme synthesis. The most common adverse effects are abdominal pain, hyperhidrosis, and nausea. Due to lack of available data, *triclabendazole* should be used with caution in pregnancy.

IV. DRUGS FOR THE TREATMENT OF CESTODES

The cestodes, or "true tapeworms," typically have a flat, segmented body and attach to the host's intestine (Figure 36.6). Like the trematodes, the tapeworms lack a mouth and a digestive tract throughout their life cycle.

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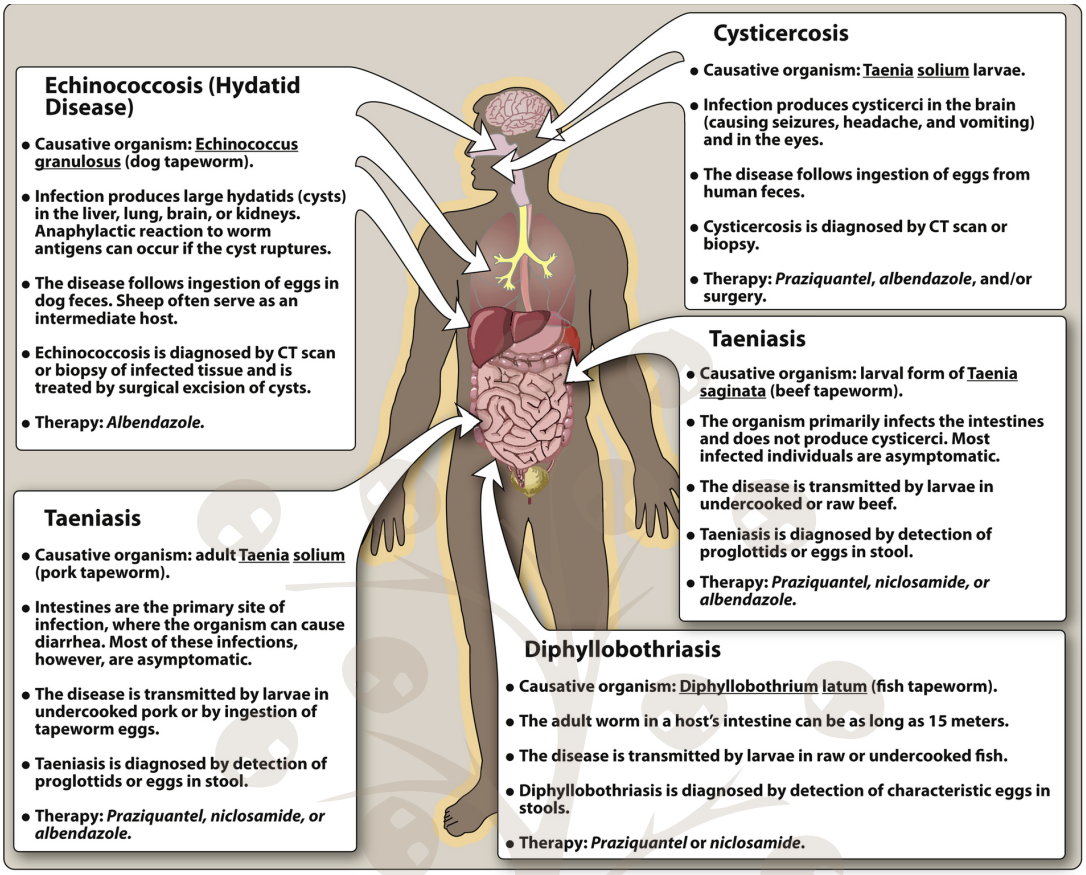

Figure 36.6 Characteristics of and therapy for commonly encountered cestode infections.CT = computed tomography.

A. Niclosamide

Niclosamide [ni-KLOE-sa-mide] (no longer available in the United States) is an alternative to *praziquantel* for the treatment of taeniasis, diphyllobothriasis, and other cestode infections. It inhibits the mitochondrial phosphorylation of adenosine diphosphate in the parasite, making it lethal for the cestode's scolex and segments but not for the ova. A laxative is administered prior to oral administration to purge the bowel of all dead segments and to enhance digestion and liberation of the ova. Alcohol should be avoided within 1 day of *niclosamide* use.

B. Albendazole

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Albendazole [al-BEN-da-zole], another benzimidazole, inhibits microtubule synthesis and glucose uptake in nematodes and is effective against most nematodes known. Its primary therapeutic application, however, is in the treatment of cestodal infestations, such as cysticercosis and hydatid disease (caused by larval stage of *Echinococcus granulosus*). [Note: *Albendazole* is also very effective in treating microsporidiosis, a fungal infection.] *Albendazole* is erratically absorbed after oral administration, but absorption is enhanced by a high-fat meal. It undergoes extensive first-pass metabolism in the liver, including formation of an active sulfoxide, and its metabolites are primarily excreted in the bile. When used in short-course therapy (1-3 days) for nematodal infestations, adverse effects are mild and transient and include headache and nausea. Treatment of hydatid disease (3 months) has a risk of hepatotoxicity and, rarely, agranulocytosis or pancytopenia; due to this, it is recommended to monitor blood counts and liver function tests every 2 weeks while on *albendazole* therapy. Medical treatment of neurocysticercosis is associated with inflammatory responses to dying parasites in the central nervous system, including headache, vomiting, fever, and seizures.

Chapter Summary

- The helminth class of organisms can be divided into three major groups: nematodes, trematodes, and cestodes.
- Options for the treatment of nematodal infections include *ivermectin*, *moxidectin*, *albendazole*, *pyrantel pamoate*, *mebendazole*, and *diethylcarbamazine.*
- Options for the treatment of trematodal infections include *praziquantel* (most infections) and *triclabendazole* (treatment of fascioliasis).
- Options for the treatment of cestodal infections include *albendazole*, *praziquantel*, and *niclosamide.*
- Many anthelmintics are not safe for use in pregnancy.

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STUDY QUESTIONS

Choose the ONE best answer.

36.1 A 32-year-old man is diagnosed with whipworm disease after he spent the summer working outside without shoes. Which of the following would be the best treatment option?

A. Pyrantel pamoate
B. Mebendazole
C. Triclabendazole
D. Diethylcarbamazine

Correct answer = B. Mebendazole is a preferred treatment for nematode infection with whipworm. Pyrantel pamoate is used for the treatment of hookworms and pinworms. Triclabendazole is indicated for the treatment of fascioliasis, and diethylcarbamazine is used for filariasis.

36.2 Which of the following statements best describes the mechanism of action of pyrantel pamoate?

A. Acts as a depolarizing neuromuscular blocking agent leading to paralysis of the worm
B. Binds to β-tubulin and inhibits the assembly of the microtubules polymerization in the parasite
C. Inhibits the mitochondrial phosphorylation of adenosine diphosphate (ADP) in the parasite
D. Inhibits glucose uptake leading to parasite death

Correct answer = A. Pyrantel pamoate acts as a depolarizing neuromuscular blocking agent, causing release of acetylcholine and inhibition of cholinesterase, leading to paralysis and intestinal expulsion of the worm.

36.3 Which of the following is the best treatment option for treatment of cutaneous larva migrans?

A. Pyrantel pamoate

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B. Diethylcarbamazine
C. Ivermectin
D. Niclosamide

Correct answer = C. Ivermectin is the drug of choice for the treatment of cutaneous larva migrans, which is usually self-limiting; however, treatment will shorten the course of the disease.

36.4 Which of the following drugs used to treat river blindness targets chloride channels and can cause a Mazzotti reaction?

A. Moxidectin
B. Praziquantel
C. Pyrantel pamoate
D. Albendazole

Correct answer = A. Moxidectin targets the parasite's glutamate-gated chloride channel receptors. Chloride influx and hyperpolarization occur, resulting in paralysis of the worm. The killing of the microfilaria in onchocerciasis can result in a dangerous Mazzotti reaction. This can happen with ivermectin, moxidectin, or diethylcarbamazine.

36.5 A 48-year-old tourist from Mexico presents with seizures and other neurologic symptoms. Eggs of *Taenia solium* are found in a stool specimen. Magnetic resonance imaging of the brain shows many cysts, some of which are calcified. Which of the following drugs would be of benefit to this individual?

A. Ivermectin
B. Pyrantel pamoate
C. Albendazole
D. Diethylcarbamazine

Correct answer = C. The symptoms and other findings for this patient are consistent with neurocysticercosis. Albendazole is the drug of choice for the treatment of this infestation. The other drugs are not effective against the larval forms of tapeworms.

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36.6 A 37-year-old man presents with diarrhea and gastrointestinal bleeding. Eggs of *Schistosoma mansoni* are found upon examination of a stool specimen. The patient has a history of seizures and is currently on phenytoin. Metabolism of which medication will be increased due to his current drug regimen?

A. Ivermectin
B. Praziquantel
C. Moxidectin
D. Niclosamide

Correct answer = B. Phenytoin, rifampin, and carbamazepine may increase the metabolism of praziquantel. Praziquantel is the treatment of choice for schistosomiasis.

36.7 When used for longer treatment, such as hydatid disease, which medication is associated with risks of hepatotoxicity and agranulocytosis?

A. Albendazole
B. Diethylcarbamazine
C. Niclosamide
D. Ivermectin

Correct answer = A. When used in short-course therapy, albendazole is associated with adverse effects such as headache and nausea. When used for the treatment of hydatid disease (3 months), there is a risk of hepatotoxicity and, rarely, agranulocytosis or pancytopenia.

36.8 Which of the following agents is the most appropriate treatment of filariasis?

A. Albendazole
B. Diethylcarbamazine
C. Praziquantel

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D. Triclabendazole

Correct answer = B. Diethylcarbamazine is the preferred treatment for filariasis caused by infection with Wuchereria bancrofti, Brugia malayi, or Brugia timori. It kills the microfilariae and has activity against adult worms. Albendazole may be used in mass treatment regimens to prevent filariasis. Praziquantel and triclabendazole are not used in the treatment of filariasis.

36.9 Which of the following medications is contraindicated with mebendazole?

A. Dexamethasone
B. Rifampin
C. Metronidazole
D. Niclosamide

Correct answer = C. Concurrent use of metronidazole and mebendazole increases the risk of severe adverse reactions such as Stevens–Johnson syndrome or toxic epidermal necrolysis.

36.10 Which of the following agents is the most appropriate treatment for fascioliasis?

A. Triclabendazole
B. Ivermectin
C. Praziquantel
D. Niclosamide

Correct answer = A. Triclabendazole is currently the only treatment option for fascioliasis. The other agents do not have an indication for fascioliasis. Praziquantel is the treatment of choice for most other trematode infections (with the exception of fascioliasis).

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37

Anticancer Drugs

Kelly M. Quesnelle

I. OVERVIEW

It is estimated that over 25% of the population of the United States will face a diagnosis of cancer during their lifetime, with more than 1.6 million new cancer patients diagnosed each year. Less than a quarter of these patients will be cured solely by surgery and/or local radiation. Most of the remainder will receive systemic chemotherapy at some time during their illness. In a small fraction (approximately 10%) of patients with cancer representing selected neoplasms, chemotherapy will result in a cure or a prolonged remission. However, in most cases, drug therapy will produce only a regression of the disease, and complications and/or relapse may eventually lead to death. Thus, the overall 5-year survival rate for cancer patients is about 68%, ranking cancer second only to cardiovascular disease as a cause of mortality. Figure 37.1 provides a list of the anticancer agents discussed in this chapter.

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ANTIMETABOLITES

Azacitidine VIDAZA, ONUREG
Capecitabine XELODA
Cladribine GENERIC ONLY
Cytarabine DEPOCYT, CYTOSAR
Fludarabine GENERIC ONLY
5-Fluorouracil CARAC, EFUDEX, FLUOROPEX
Gemcitabine INFUGEM
6-Mercaptopurine PURIXAN
Methotrexate **(MTX)** TREXALL
Pemetrexed ALIMTA
Pralatrexate FOLOTYN

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ANTIBIOTICS

Bleomycin GENERIC ONLY
Daunorubicin CERUBIDINE
Doxorubicin ADRIAMYCIN, DOXIL
Epirubicin ELLENCE
Idarubicin IDAMYCIN
Mitoxantrone GENERIC ONLY

ALKYLATING/ADDUCTING AGENTS

Busulfan MYLERAN, BUSULFEX
Carboplatin GENERIC ONLY
Carmustine BICNU, GLIADEL WAFER
Chlorambucil LEUKERAN
Cisplatin GENERIC ONLY
Cyclophosphamide GENERIC ONLY
Dacarbazine GENERIC ONLY
Ifosfamide IFEX
Lomustine GLEOSTINE
Melphalan ALKERAN, EVOMELA
Oxaliplatin ELOXATIN
Temozolomide TEMODAR

MICROTUBULE INHIBITORS

Docetaxel TAXOTERE
Paclitaxel GENERIC ONLY
Vinblastine GENERIC ONLY
Vincristine GENERIC ONLY
Vinorelbine NAVELBINE

STEROID HORMONES AND THEIR ANTAGONISTS

Anastrozole ARIMIDEX
Apalutamide ERLEADA
Bicalutamide CASODEX
Darolutamide NUBEQA
Exemestane AROMASIN
Flutamide GENERIC ONLY
Fulvestrant FASLODEX
Goserelin ZOLADEX
Letrozole FEMARA
Leuprolide LUPRON, ELIGARD
Nilutamide NILANDRON
Raloxifene EVISTA
Tamoxifen SOLTAMOX
Triptorelin TRELSTAR

MONOCLONAL ANTIBODIES

Bevacizumab AVASTIN
Brentuximab ADCETRIS

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Cetuximab ERBITUX
Panitumumab VECTIBIX
Rituximab RITUXAN
Trastuzumab HERCEPTIN

KINASE INHIBITORS

Afatinib GILOTRIF
Crizotinib XALKORI
Dasatinib SPRYCEL
Erdafitinib BALVERSA
Erlotinib TARCEVA
Ibrutinib IMBRUVICA
Idelalisib ZYDELIG
Imatinib GLEEVEC
Lapatinib TYKERB
Midostaurin RYDAPT
Pralsetinib GAVRETO
Ruxolitinib JAKAVI
Sorafenib NEXAVAR
Trametinib MEKINIST
Vemurafenib ZELBORAF

IMMUNOTHERAPIES

Atezolizumab TECENTRIQ
Avelumab BAVENCIO
Ipilimumab YERVOY
Nivolumab OPDIVO
Pembrolizumab KEYTRUDA

CELLULAR AND GENE THERAPIES

Tisagenlecleucel KYMRIAH
Axicabtagene ciloleucel YESCARTA
Lisocabtagene maraleucel BREYANZI
Brexucabtagene autoleucel TECARTUS
Sipuleucel-T PROVENGE

POLE STAR

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Figure 37.1 Summary of chemotherapeutic agents.

II. PRINCIPLES OF CANCER CHEMOTHERAPY

Cancer chemotherapy strives to cause apoptosis or a lethal cytotoxic event in the cancer cells that can arrest the progression of tumor growth. The attack is generally directed toward DNA or against metabolic pathways essential to cell replication, for example, the availability of purines and pyrimidines, which are the building blocks for DNA or RNA synthesis (Figure 37.2). The ideal anticancer drug would interfere only

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with cellular processes that are unique to malignant cells. Unfortunately, most traditional anticancer drugs do not recognize neoplastic cells specifically but, rather, affect all kinds of proliferating cells. Therefore, almost all antitumor agents have a steep dose–response curve for both therapeutic and toxic effects. Targeted therapies specific for kinases or growth factors that are abundant in tumor cells may have a reduced adverse effect profile. Newer agents are being developed that take a different approach to cancer treatment by blocking cell-cycle checkpoints and allowing the patient's own immune system to attack cancer cells. While this strategy is showing great promise, adverse effects remain a concern and present as autoimmune toxicity, as compared with the myelosuppressive toxicities that occur with traditional chemotherapy agents.

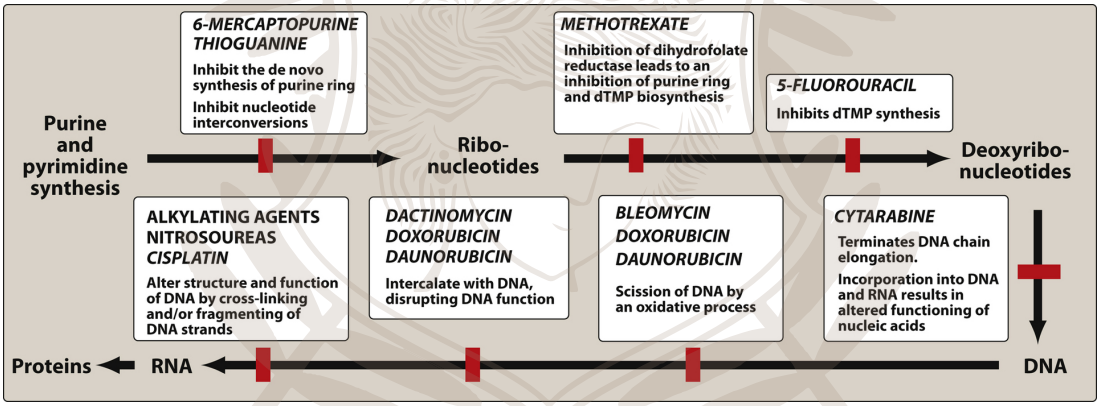

Figure 37.2 Examples of chemotherapeutic agents affecting RNA and DNA.dTMP = deoxythymidine monophosphate.

A. Goals of treatment

The ultimate goal of chemotherapy is a cure (long-term, disease-free survival). A true cure requires the eradication of every neoplastic cell. In some cases, a cure is not attainable, so the goal becomes control of the disease (prevent the cancer from enlarging and spreading) to extend survival and maintain quality of life. A patient can maintain a "near-normal" existence with the cancer treated as a chronic disease. In either case, the neoplastic cell burden is often reduced (debulked), either by surgery and/or by radiation, followed by chemotherapy,

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immunotherapy, therapy using biological modifiers, or a combination of these treatment modalities (Figure 37.3). In advanced stages of cancer, the likelihood of controlling the cancer is low, and the goal is palliation (alleviation of symptoms and avoidance of life-threatening toxicity). This means that chemotherapeutic drugs may be used to relieve symptoms caused by the cancer and improve the quality of life, even though the drugs may not extend survival. The goal of treatment should always be kept in mind, as it often influences treatment decisions. Figure 37.4 illustrates how treatment goals can be dynamic.

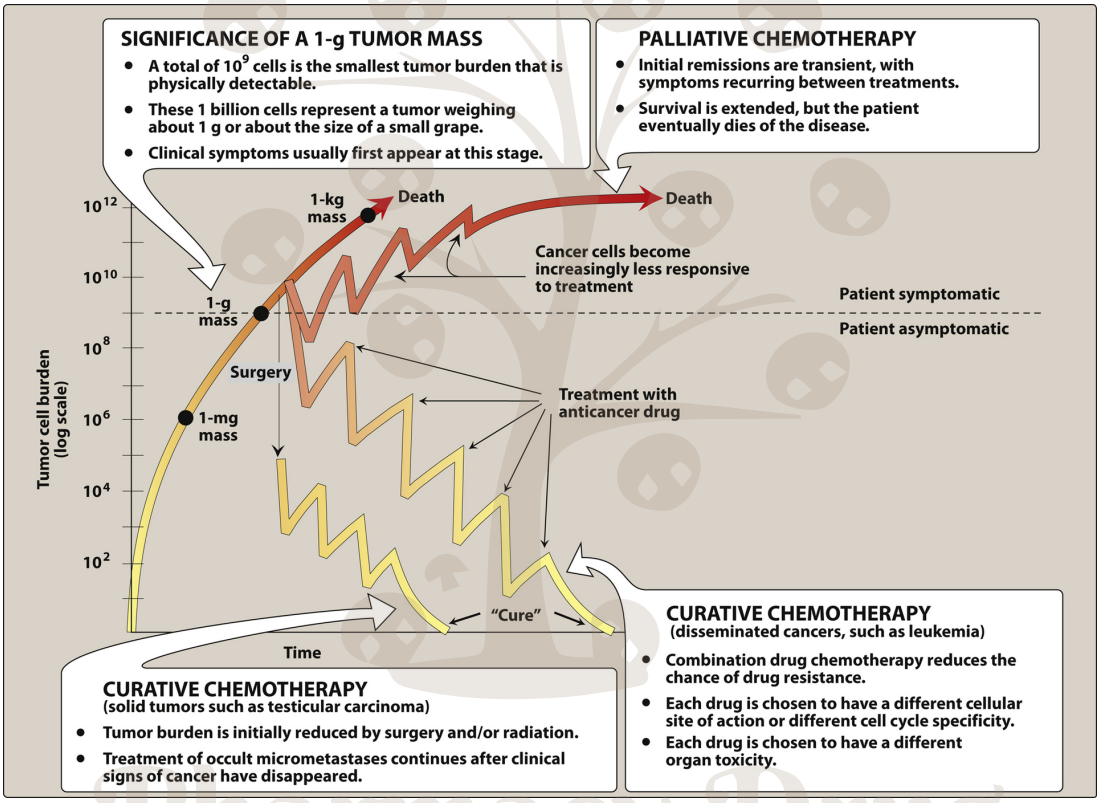

Figure 37.3 Effects of various treatments on the cancer cell burden in a hypothetical patient.

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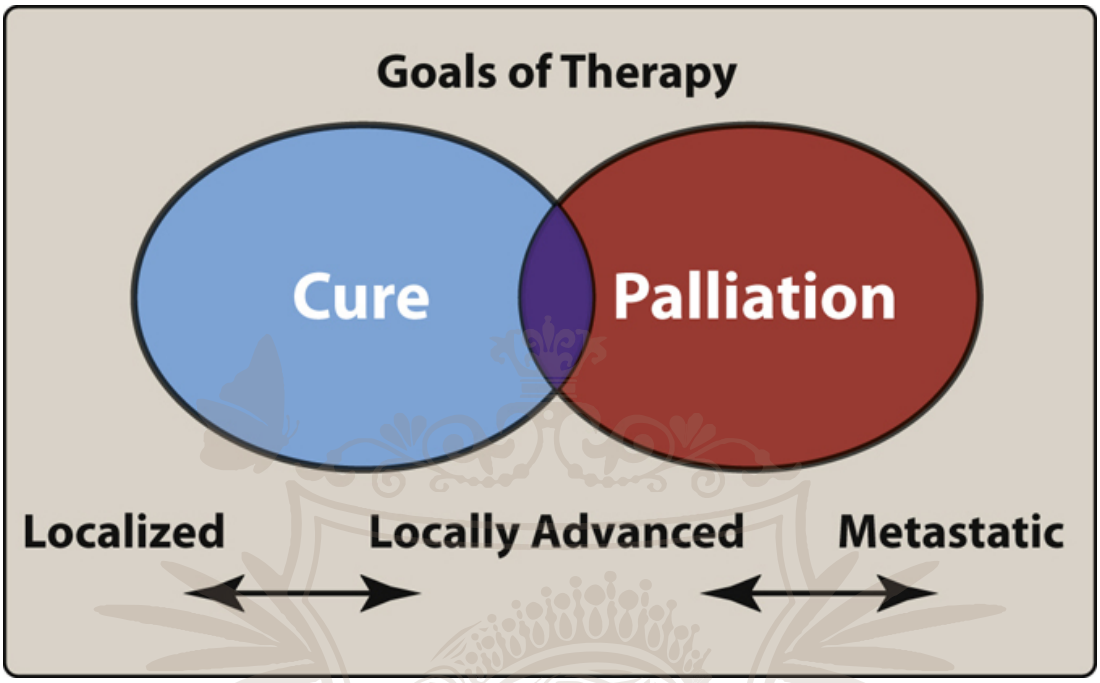

Figure 37.4 Goals of treatment with chemotherapeutic agents.(Reprinted from Dr. Thomas George, MD, with permission.)

B. Indications for treatment

Chemotherapy is sometimes used when neoplasms are disseminated and are not amenable to surgery. Chemotherapy may also be used as a supplemental treatment to attack micrometastases following surgery and radiation treatment, in which case it is called **adjuvant** chemotherapy. Chemotherapy given prior to the surgical procedure in an attempt to shrink the cancer is referred to as **neoadjuvant** chemotherapy, and chemotherapy given in lower doses to assist in prolonging remission is known as **maintenance** chemotherapy.

C. Chemotherapy regimens

Combination chemotherapy is more successful than single-drug treatment in most cancers for which chemotherapy is effective.

1.Combination chemotherapy: Cytotoxic agents with different toxicities, and with different molecular sites and mechanisms of action, are usually combined at full doses. This results in higher response rates, due to additive and/or potentiated

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cytotoxic effects, and nonoverlapping host toxicities. In contrast, agents with similar dose-limiting toxicities, such as myelosuppression, nephrotoxicity, or cardiotoxicity, can be combined safely only by reducing the doses of each. The advantages of combination chemotherapy are that it (1) provides maximal cell killing within the range of tolerated toxicity, (2) is effective against a broader range of cell lines in the heterogeneous tumor population, and (3) may delay or prevent the development of resistant cell lines.

2.Treatment protocols: Many cancer treatment protocols have been developed, and each is applicable to a particular neoplastic state. They are usually identified by an acronym. For example, a common regimen called R-CHOP, used for the treatment of non-Hodgkin lymphoma, consists of ***r*** *ituximab,* ***c*** *yclophosphamide*, ***h*** *ydroxydaunorubicin (doxorubicin),* ***O*** *ncovin* (*vincristine*), and ***p*** *rednisone.* Therapy is scheduled intermittently to allow recovery or rescue of the immune system, which is also affected by the chemotherapeutic agents, thus reducing the risk of serious infection. Drug dosages are usually calculated on the basis of body surface area, in an effort to tailor the dosage to each patient.

D. Tumor susceptibility and the growth cycle

The fraction of tumor cells that are in the replicative cycle (“growth fraction”) influences tumor susceptibility to most chemotherapeutic agents. Rapidly dividing cells are generally more sensitive to chemotherapy, whereas slowly proliferating cells are less sensitive to chemotherapy.

Nondividing cells (those in the G_0 phase; Figure 37.5) usually survive the toxic effects of many chemotherapeutic agents.

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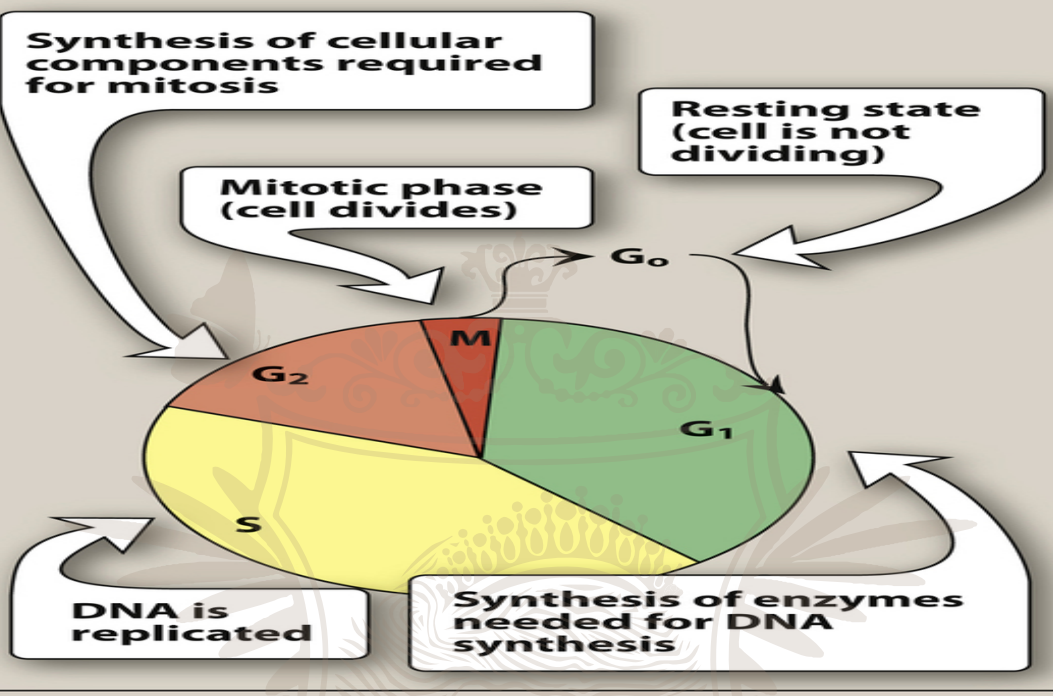
A The cell cycle



B Cell cycle–specific drugs

Antimetabolites
Bleomycin
Etoposide
Vinca alkaloids

Effective for high-growth-fraction malignancies such as hematologic cancers

C Cell cycle non-specific drugs

Alkylating agents
Antibiotics
Cisplatin
Nitrosoureas

Effective for both low-growth-fraction malignancies, such as solid tumors, as well as high-growth-fraction malignancies

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Figure 37.5 Effects of chemotherapeutic agents on the growth cycle of mammalian cells.

1.Cell cycle specificity of drugs: Both normal cells and tumor cells go through growth cycles (Figure 37.5). However, the number of cells that are in various stages of the cycle may differ in normal and neoplastic tissues. Chemotherapeutic agents that are effective only against replicating cells (that is, those cells that are dividing) are said to be cell cycle specific (Figure 37.5), whereas other agents are cell cycle nonspecific. Although the nonspecific drugs generally have greater toxicity in cycling cells, they are also useful against tumors that have a low percentage of replicating cells. Examples of cell cycle–specific agents include the antimetabolites, taxanes, and vinca alkaloids. Examples of non-cell cycle–specific agents include the alkylating agents.

2.Tumor growth rate: The growth rate of most solid tumors is initially rapid, but growth rate usually decreases as the tumor size increases (see Figure 37.3). This is due to a deficiency of nutrients and oxygen caused by inadequate vascularization and lack of blood circulation. Tumor burden can be reduced through surgery, radiation, or use of cell cycle–nonspecific drugs that promote the remaining cells into active proliferation, thus increasing susceptibility to cell cycle–specific chemotherapeutic agents.

E. Log kill phenomenon

Destruction of cancer cells by chemotherapeutic agents follows first-order kinetics (that is, a given dose of drug destroys a constant fraction of cells). The term “log kill” is used to describe this phenomenon. For example, a diagnosis of leukemia is generally made when there are about 10^9 (total) leukemic cells. Consequently, if treatment leads to a 99.999% kill, then 0.001% of 10^9 cells (or 10^4 cells) remain. This is defined as a 5-log kill (reduction of 10^5 cells). At this point, the patient becomes asymptomatic, and the patient is in remission (see Figure 37.3). For most bacterial infections, a 5-log (100,000-fold) reduction in the number of microorganisms results in a cure, because the immune system can destroy the remaining bacterial cells. However, tumor cells are not as readily eliminated, and

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additional treatment is required to totally eradicate the leukemic cell population.

F. Pharmacologic sanctuaries

Leukemic or other tumor cells find sanctuary in tissues such as the central nervous system (CNS), where transport constraints prevent certain chemotherapeutic agents from entrance. Therefore, a patient may require irradiation of the craniospinal axis or intrathecal administration of drugs to eliminate leukemic cells at that site. Similarly, drugs may be unable to penetrate certain areas of solid tumors.

G. Resistance to chemotherapy

Cancer drugs are toxins that present a lethal threat to the cells. It is, therefore, not surprising that cells have evolved elaborate defense mechanisms to protect themselves from chemical toxins, including chemotherapeutic agents.

1.Resistance: Some neoplastic cells (for example, melanoma) are inherently resistant to most anticancer drugs. Other tumor types may acquire resistance to the cytotoxic effects of a drug by mutating, particularly after prolonged administration of suboptimal doses. The development of drug resistance is minimized by short-term, intensive, intermittent therapy with combinations of drugs. Drug combinations are also effective against a broader range of resistant cells in the tumor population.

2.Multidrug resistance: Stepwise selection of an amplified gene that codes for a transmembrane protein (P-glycoprotein for "permeability" glycoprotein; Figure 37.6) is responsible for multidrug resistance. This resistance is due to adenosine triphosphate–dependent pumping of drugs out of the cell in the presence of P-glycoprotein. Cross-resistance following the use of structurally unrelated agents also occurs. For example, cells that are resistant to the cytotoxic effects of the vinca alkaloids are also resistant to *dactinomycin* and to the anthracycline antibiotics, as well as to *colchicine* (an agent for gout), and vice versa. These drugs are all naturally occurring substances, each of which has a hydrophobic aromatic ring and a positive charge at neutral pH.

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[Note: P-glycoprotein is normally expressed at low levels in most cell types, but higher levels are found in the kidney, liver, pancreas, small intestine, colon, and adrenal gland. It has been suggested that the presence of P-glycoprotein may account for the intrinsic resistance to chemotherapy observed with adenocarcinomas.] Certain drugs at high concentrations (for example, *verapamil*) can inhibit the pump and, thus, interfere with the efflux of the anticancer agent. However, these drugs are undesirable because of adverse pharmacologic actions of their own. Pharmacologically inert pump blockers are being sought.

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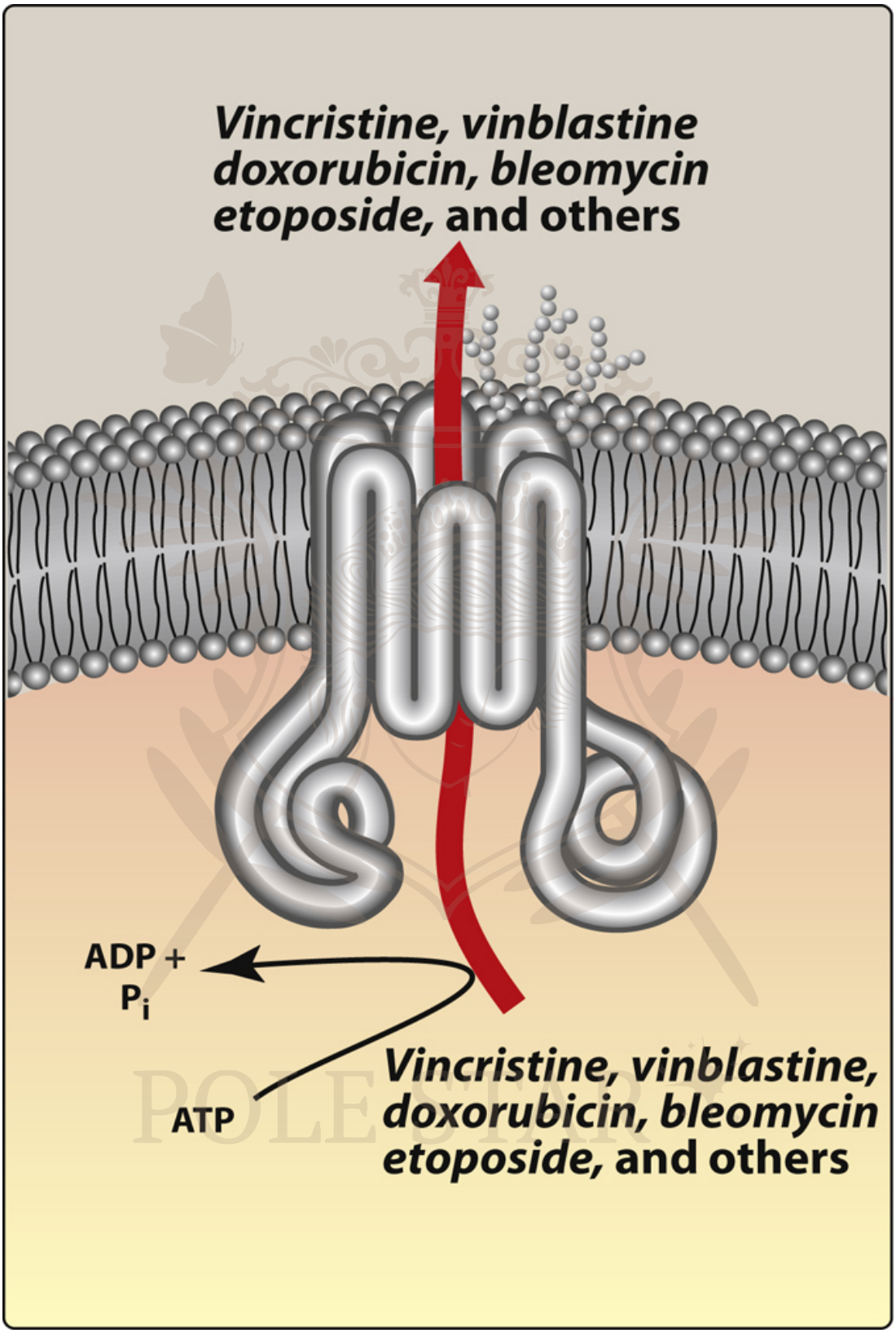
Vincristine, vinblastine
doxorubicin, bleomycin
etoposide, and others
ADP +
P_i
ATP
Vincristine, vinblastine,
doxorubicin, bleomycin
etoposide, and others

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Figure 37.6 The six membrane-spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping of drugs from the cell.Modified from N.Kartner and V.Ling . Multidrug resistance in cancer. *Sci. Am*. (1989).

H. Adverse effects of chemotherapy

Therapy aimed at killing rapidly dividing cancer cells also affects normal cells undergoing rapid proliferation such as cells of the buccal mucosa, bone marrow, gastrointestinal (GI) mucosa, and hair follicles. This may contribute to the toxic manifestations of chemotherapy.

1.Common adverse effects: Most chemotherapeutic agents have a narrow therapeutic index. Severe vomiting, stomatitis, bone marrow suppression, and alopecia occur to varying extents with most antineoplastic agents. Vomiting is often controlled by administration of antiemetic drugs (see Chapter 42). Some toxicities, such as myelosuppression that predisposes patients to infection, are common to many chemotherapeutic agents (Figure 37.7), and prophylactic antimicrobials should be considered based on evidence-based guidelines. Other adverse reactions are confined to specific agents, such as bladder toxicity with *ifosfamide,* cardiotoxicity with *doxorubicin*, and pulmonary fibrosis with *bleomycin.* The duration of the adverse effects varies widely. For example, alopecia is transient, but cardiac, pulmonary, and bladder toxicities can be irreversible. Tumor lysis syndrome is an oncologic emergency caused by massive tumor cell lysis that occurs in tumors with a high proliferative rate or high sensitivity to cytotoxic therapy (for example, Burkitt lymphoma, T-cell acute lymphoblastic leukemia). It can lead to many metabolic disturbances, including hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia.

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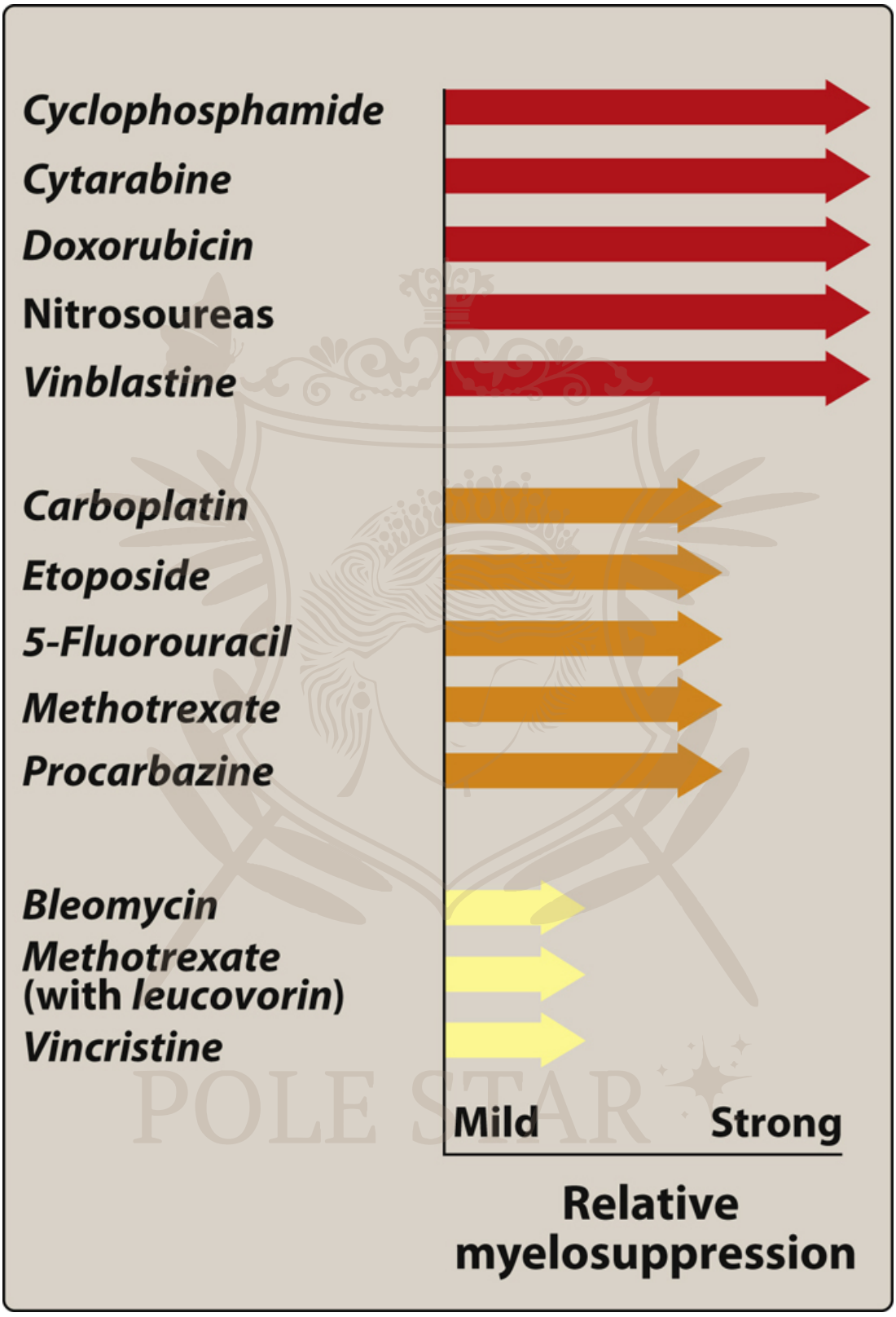

POLE STAR

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Figure 37.7 Comparison of myelosuppressive potential of chemotherapeutic drugs.

2.Minimizing adverse effects: Some toxic reactions may be ameliorated by interventions, such as the use of cytoprotectant drugs, local perfusion of the tumor (for example, a sarcoma of the arm), or intensive hydration and diuresis to prevent bladder toxicities. For example, the megaloblastic anemia that occurs with *methotrexate* can be effectively counteracted by administering *folinic acid* (*leucovorin*), and the drug *mesna* can bind a toxic metabolite of *ifosfamide* to reduce the potential for hemorrhagic cystitis. Granulocyte colony-stimulating factors can be administered to increase the production of neutrophils and reduce the risk of neutropenic fevers caused by chemotherapy (see Chapter 44).

3.Treatment-induced tumors: Because most antineoplastic agents are mutagens, and may cause changes in DNA, neoplasms such as acute myelogenous leukemia may arise anytime up to 10 or more years after the original cancer is cured. Unfortunately, most tumors that develop from cancer chemotherapeutic agents do not respond well to treatment strategies.

Clinical Application 37.1: Secondary Malignancies

Some of the agents used to treat cancer may also cause cancer. Adducting agents, such as the platinum-containing drugs (for example, *cisplatin* and *carboplatin*), and topoisomerase inhibitors (for example, *etoposide*), are known to cause secondary malignancies like acute myeloid leukemia (AML) and acute lymphocytic leukemia. Therapy-related AML can be difficult to cure, in part because it tends to present with cytogenetics that are associated with poor outcomes.

III. ANTIMETABOLITES

Antimetabolites are structurally related to normal compounds that exist within the cell. They generally interfere with the availability of normal

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purine or pyrimidine nucleotide precursors, either by inhibiting their synthesis or by competing with them in DNA or RNA synthesis. Their maximal cytotoxic effects are in S phase and are, therefore, cell cycle specific. A summary of important characteristics and adverse effects of the antimetabolites is provided in Figure 37.8.

DRUG	ROUTE	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
Methotrexate	IV/PO/ IM/IT	N/V/D, stomatitis, rash, alopecia, myelosuppression, high-dose: renal damage IT: neurologic toxicities	*Omeprazole, folic acid, warfarin*, NSAIDs, penicillins, cephalosporins	CBC; renal, hepatic function; *methotrexate* levels (after high-dose infusion)	Some adverse effects can be prevented or reversed by administering *leucovorin*. Adjust dose in renal impairment.
6-Mercaptopurine (6-MP)	PO	N/V/D, myelosuppression, anorexia, hepatotoxicity (jaundice)	*Warfarin, allopurinol*, SMX/TMP	CBC; renal, hepatic function	Reduce dose of *6-MP* by 50%–75% when used with *allopurinol* to prevent toxicity
Fludarabine	IV	N/V/D, myelosuppression, rash, immunosuppression, fever, edema, neurologic toxicity	*Cytarabine, cyclophosphamide, cisplatin, mitoxantrone, pentostatin*	CBC; renal, hepatic function; tumor lysis syndrome	Immunosuppression increases risk of opportunistic infections. Adjust dose in renal impairment.
Cladribine	IV/SC	Neutropenia, immunosuppression, fever, N/V, teratogenic, peripheral neuropathy		CBC; renal function; tumor lysis syndrome	Immunosuppression increases risk of opportunistic infections.
5-Fluorouracil (5-FU)	IV	D, alopecia, severe mucositis, myelosuppression (bolus), "hand-foot syndrome" (continuous infusion), coronary vasospasm	*Methotrexate* (antifolate analogs)	CBC; renal, hepatic function; D	"Hand-foot syndrome"/palmar-plantar erythrodysesthesia is an erythematous desquamation of the palms and soles.
Capecitabine	PO	D, mucositis, myelosuppression, "hand-foot syndrome," chest pain	*Warfarin, phenytoin*	CBC; renal, hepatic function; D	Should be taken within 30 min of a meal; keep skin well moisturized.
Cytarabine	IV/IT	N/V/D, myelosuppression, hepatotoxicity; neurologic toxicity, conjunctivitis (high dose)	*Digoxin*, alkylating agents, *methotrexate*	CBC; renal, hepatic function; CNS toxicity	Administer steroid eye drops with high dose to prevent conjunctivitis.
Azacitidine	IV/SC	Myelosuppression (neutropenia, thrombocytopenia), N/V, constipation, hypokalemia, renal toxicity		CBC; renal, hepatic function	Stability of prepared drug (IV) is only 60 min.
Gemcitabine	IV	Myelosuppression, (thrombocytopenia), N/V, alopecia, rash, flu-like syndrome	Potent radiosensitizer	CBC; hepatic function, rash	

Figure 37.8 Summary of antimetabolites.CBC = complete blood count; CNS = central nervous system; D = diarrhea; IM = intramuscular; IT = intrathecal; IV = intravenous; N = nausea; NSAID = nonsteroidal anti-inflammatory drug; PO = oral; SC = subcutaneous; SMX/TMP = *sulfamethoxazole/trimethoprim*; V = vomiting.

POLE STAR

A. Methotrexate, pemetrexed, and pralatrexate

The vitamin folic acid plays a central role in a variety of metabolic reactions involving the transfer of one-carbon units and is essential for cell replication. Folic acid is obtained mainly from dietary sources and intestinal flora. *Methotrexate* [meth-oh-TREK-sate] (*MTX*), *pemetrexed*

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[pem-e-TREX-ed], and *pralatrexate* [pral-a-TREX-ate] are antifolate agents.

1.Mechanism of action: *MTX* is structurally related to folic acid and acts as an antagonist of the vitamin by inhibiting mammalian dihydrofolate reductase (DHFR), the enzyme that converts folic acid to its active, coenzyme form, tetrahydrofolic acid (FH_4) (Figure 37.9). The inhibition of DHFR can only be reversed by a 1000-fold excess of the natural substrate, dihydrofolate (FH_2), or by administration of *leucovorin,* which bypasses the blocked enzyme and replenishes the folate pool (Figure 37.9). [Note: *Leucovorin*, or *folinic acid*, is the N^5-formyl group–carrying form of FH_4.] *MTX* is specific for the S phase of the cell cycle. *Pemetrexed* is an antimetabolite similar in mechanism to *methotrexate.* However, in addition to inhibiting DHFR, it also inhibits thymidylate synthase and other enzymes involved in folate metabolism and DNA synthesis. *Pralatrexate* is an antimetabolite that also inhibits DHFR.

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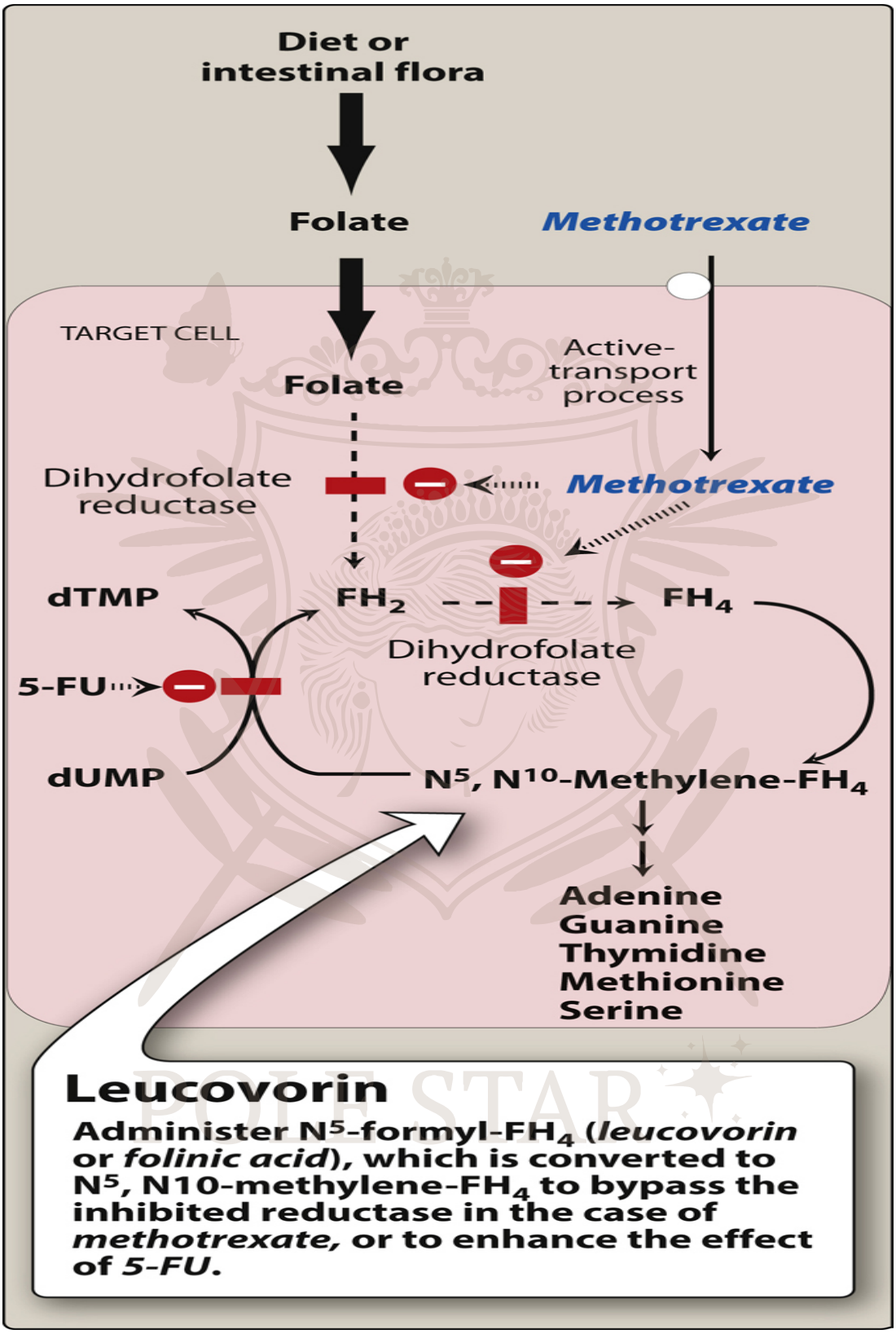
Diet or intestinal flora
Folate
Methotrexate
TARGET CELL
Folate
Active-transport process
Dihydrofolate reductase
Methotrexate
dTMP
FH2
FH4
Dihydrofolate reductase
5-FU
dUMP
N5, N10-Methylene-FH4
Adenine
Guanine
Thymidine
Methionine
Serine
Leucovorin
Administer N5-formyl-FH4 (leucovorin or folinic acid), which is converted to N5, N10-methylene-FH4 to bypass the inhibited reductase in the case of methotrexate, or to enhance the effect of 5-FU.

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Figure 37.9 Mechanism of action of *methotrexate* and the effect of administration of *leucovorin*.dTMP = deoxythymidine monophosphate; dUMP = deoxyuridine monophosphate; FH_2 = dihydrofolate; FH_4 = tetrahydrofolate.

2.Therapeutic uses: *MTX*, usually in combination with other drugs, is effective against many different types of cancer, including, but not limited to, acute lymphocytic leukemia, Burkitt lymphoma in children, breast cancer, head and neck carcinomas, and mycosis fungoides. In addition, low-dose *MTX* is effective as a single agent against certain inflammatory diseases, such as severe psoriasis, rheumatoid arthritis, and Crohn disease. All patients receiving *MTX* require close monitoring for possible toxic effects. *Pemetrexed* is primarily used in lung cancers. *Pralatrexate* is used in relapsed or refractory T-cell lymphoma.

3.Pharmacokinetics: *MTX* is variably absorbed at low doses from the GI tract, but it can also be administered by intramuscular (IM), intravenous (IV), and intrathecal (IT) routes (Figure 37.10). Because *MTX* does not easily penetrate the blood–brain barrier, it can be administered intrathecally to destroy neoplastic cells that thrive in the sanctuary of the CNS. High concentrations of the drug are found in the intestinal epithelium, liver, and kidney, as well as in ascites and pleural effusions. *MTX is* also distributed to the skin. Small amounts of *MTX* undergo hydroxylation at the 7th position to form 7-hydroxymethotrexate. This derivative is less water soluble than *MTX* and may lead to crystalluria. Therefore, it is important to keep the urine alkaline and the patient well hydrated to avoid renal toxicity. Excretion of the parent drug and the 7-OH metabolite occurs primarily via urine.

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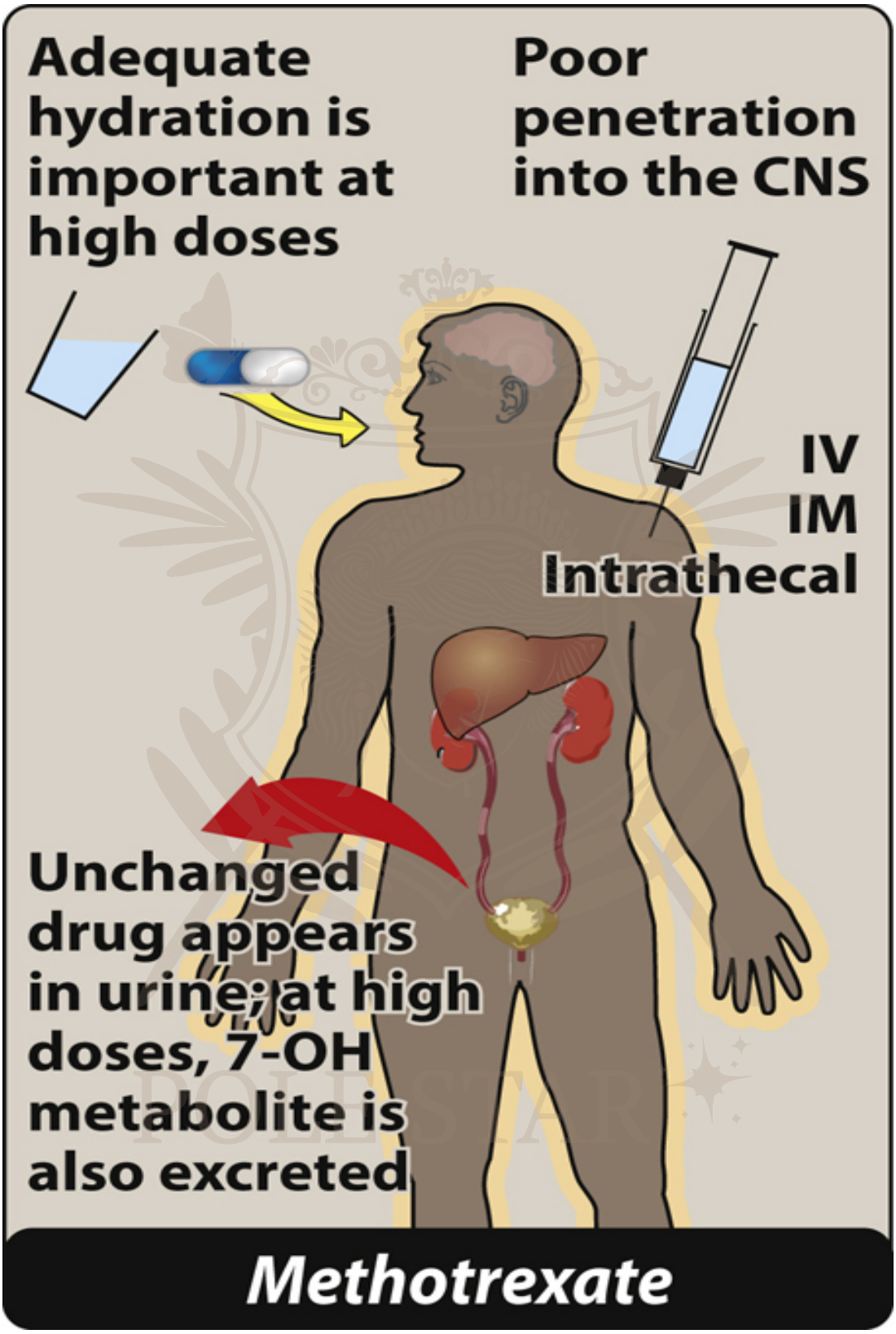
Adequate hydration is important at high doses
Poor penetration into the CNS
IV
IM
Intrathecal
Unchanged drug appears in urine; at high doses, 7-OH metabolite is also excreted
Methotrexate

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Figure 37.10 Administration and fate of *methotrexate*.CNS = central nervous system; IM = intramuscular; IV = intravenous.

4.Adverse effects: Adverse effects of *MTX* are outlined in Figure 37.8. *Leucovorin* must be added as a rescue agent with high-dose *methotrexate* treatment to decrease the risk of severe toxicity. *Pemetrexed* and *pralatrexate* should be given with folic acid and vitamin B_{12} supplements to reduce hematologic and GI toxicities. Pretreatment with corticosteroids to prevent cutaneous reactions is recommended with *pemetrexed*.

B. 6-Mercaptopurine

6-Mercaptopurine [mer-kap-toe-PYOOR-een] (*6-MP*), a purine antimetabolite, is the thiol analog of hypoxanthine. *6-MP* and *6-thioguanine* were the first purine analogs to prove beneficial for treating neoplastic disease. *Azathioprine* (see Chapter 38), an immunosuppressant, exerts its cytotoxic effects after conversion to *6-MP. 6-MP* is inactive in its parent form and gets enzymatically activated inside cells. It acts as a false metabolite and is incorporated into DNA and RNA to inhibit their synthesis. *6-MP* is used principally in the maintenance of remission in acute lymphoblastic leukemia. *6-MP* and its analog, *azathioprine*, are also beneficial in the treatment of Crohn disease.

C. Fludarabine

Fludarabine [floo-DARE-a-been] is the 5′-phosphate of 2-fluoroadenine arabinoside, a purine nucleotide analog. It is useful in the treatment of chronic lymphocytic leukemia, hairy cell leukemia, and indolent non-Hodgkin lymphoma. *Fludarabine* is a prodrug, and the phosphate is removed in the plasma to form 2-F-araA, which is taken up into cells and again phosphorylated (initially by deoxycytidine kinase). Although the exact cytotoxic mechanism is uncertain, the triphosphate is incorporated into both DNA and RNA. This decreases their synthesis in the S phase and affects their function. Resistance is associated with reduced uptake into cells, lack of deoxycytidine kinase, and decreased affinity for DNA polymerase, as well as other mechanisms.

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D. 5-Fluorouracil

5-Fluorouracil [flure-oh-YOOR-ah-sil] (*5-FU*), a pyrimidine analog, has a stable fluorine atom in place of a hydrogen atom at position 5 of the uracil ring. The fluorine interferes with the conversion of deoxyuridylic acid to thymidylic acid, thus depriving the cell of thymidine, one of the essential precursors for DNA synthesis. *5-FU* is employed primarily in the treatment of slow-growing solid tumors (for example, colorectal, breast, ovarian, pancreatic, and gastric carcinomas). When applied topically, *5-FU* is also effective for the treatment of superficial basal cell carcinomas.

1.Mechanism of action: *5-FU* itself is devoid of antineoplastic activity. It enters the cell through a carrier-mediated transport system and is converted to the corresponding deoxynucleotide (5-fluorodeoxyuridine monophosphate [5-FdUMP]; Figure 37.11), which competes with deoxyuridine monophosphate for thymidylate synthase, thus inhibiting its action. DNA synthesis decreases due to lack of thymidine, leading to imbalanced cell growth and "thymidine-less death" of rapidly dividing cells. [Note: *Leucovorin* may be used to enhance the toxicity of 5-FU by stabilizing the binding of 5-FdUMP and thymidylate synthetase. For example, a standard regimen for advanced colorectal cancer is *irinotecan* plus *5-FU/leucovorin*.] *5-FU* is also incorporated into RNA, and low levels have been detected in DNA. In the latter case, a glycosylase excises the *5-FU*, damaging the DNA. *5-FU* produces the anticancer effect in the S phase of the cell cycle.

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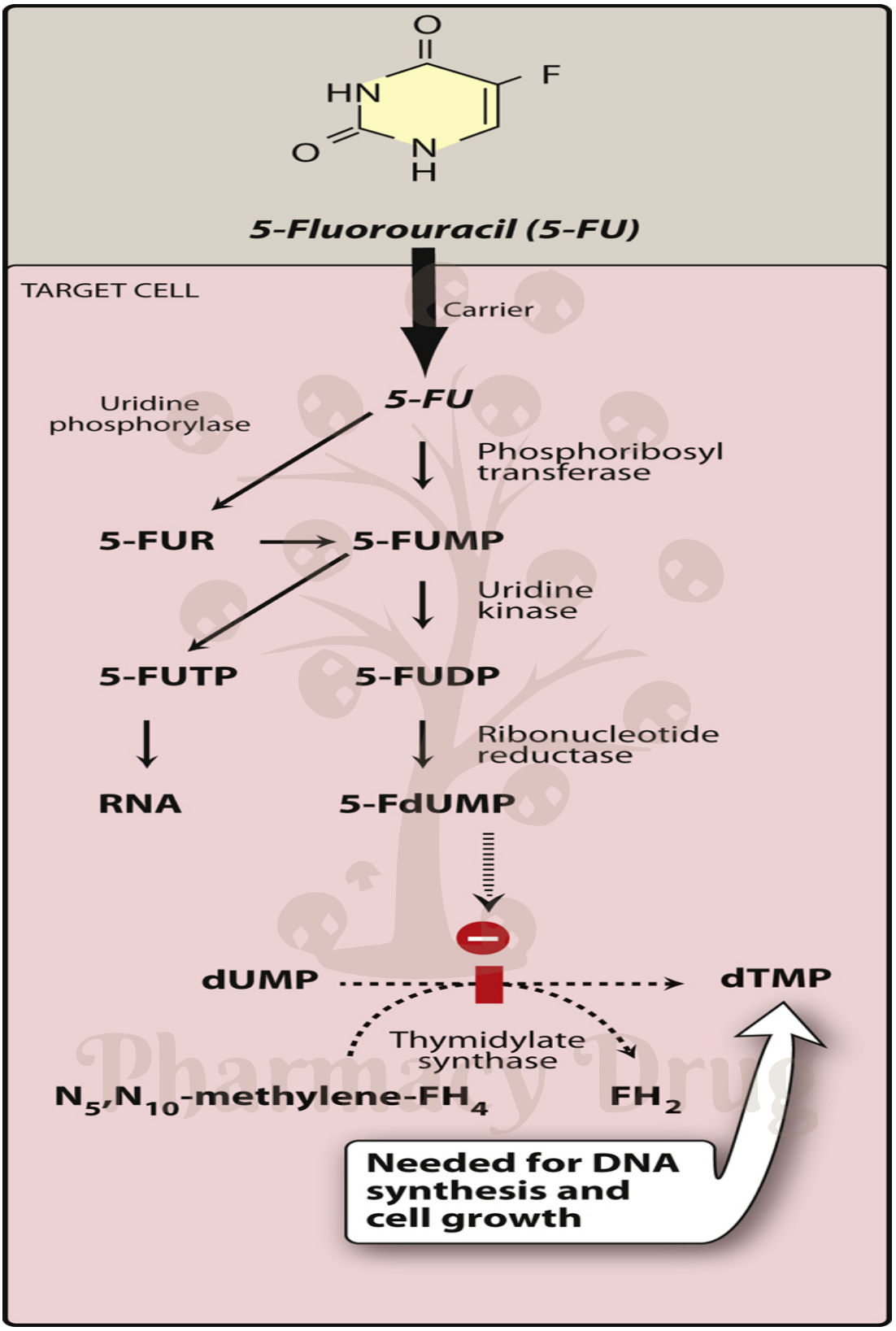

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Figure 37.11 Mechanism of the cytotoxic action of *5-FU*.*5-FU* is converted to 5-fluorodeoxyuridine monophosphate (5-FdUMP), which competes with deoxyuridine monophosphate (dUMP) for the enzyme thymidylate synthase. *5-FU* = *5-fluorouracil*; 5-FUDP = 5-fluorouridine diphosphate; 5-FUMP = 5-fluorouridine monophosphate; 5-FUR = 5-fluorouridine; 5-FUTP = 5-fluorouridine triphosphate; dTMP = deoxythymidine monophosphate. dUMP = deoxyuridine monophosphate.

2.Pharmacokinetics: Because of severe toxicity to the GI tract, *5-FU* is administered IV or, in the case of skin cancer, topically. The drug penetrates well into all tissues, including the CNS. *5-FU* is rapidly metabolized in the liver, lung, and kidney, and inactive metabolites are eliminated in the urine. Elevated levels of dihydropyrimidine dehydrogenase (DPD) can increase the rate of *5-FU* catabolism and decrease its bioavailability. The level of DPD varies from individual to individual and may differ by as much as sixfold in the general population. Patients with DPD deficiency may experience severe toxicity manifested by pancytopenia, mucositis, and life-threatening diarrhea.

E. Capecitabine

Capecitabine [KAP-e-SYE-ta-been], a fluoropyrimidine carbamate, is a prodrug of *5-fluorouracil.* It is used in the treatment of colorectal and metastatic breast cancer. *Capecitabine* is well absorbed following oral administration. After being absorbed, *capecitabine,* which is itself nontoxic, undergoes a series of enzymatic reactions, the last of which is hydrolysis to *5-FU.* This step is catalyzed by thymidine phosphorylase, an enzyme that is concentrated primarily in tumors (Figure 37.12). Thus, the cytotoxic activity of *capecitabine* is the same as that of *5-FU* and is tumor specific. The most important enzyme inhibited by *5-FU* (and, thus, *capecitabine*) is thymidylate synthase. While hand-foot syndrome (tingling, burning, redness, swelling, and blistering on the palms and soles) is more common with *capecitabine* compared with *5-FU*, other adverse effects, such as nausea, diarrhea, stomatitis, and neutropenia are reported less frequently.

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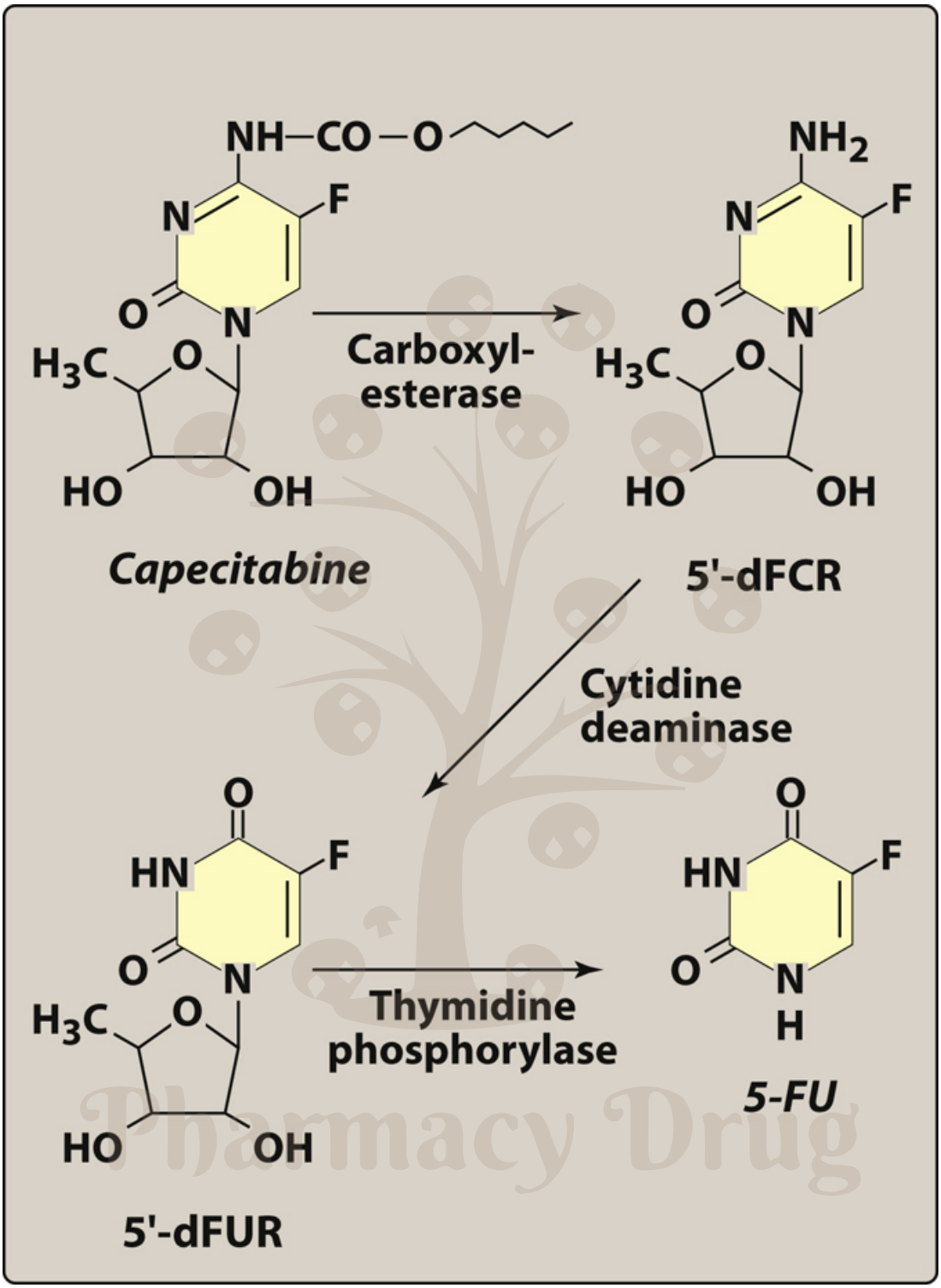

Figure 37.12 Metabolic pathway of *capecitabine* to *5-fluorouracil* (*5-FU*).5′-dFCR = 5′-deoxy-5-fluorocytidine; 5′-dFUR = 5′-deoxy-5-fluorouridine.

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F. Cytarabine

Cytarabine [sye-TARE-ah-been] (*cytosine arabinoside* or *ara-C*) is an analog of 2′-deoxycytidine in which the natural ribose residue is replaced by d-arabinose. *Cytarabine* acts as a pyrimidine antagonist. The major clinical use of *cytarabine* is in acute nonlymphocytic (myelogenous) leukemia (AML). *Cytarabine* enters the cell by a carrier-mediated process and, like the other purine and pyrimidine antagonists, must be sequentially phosphorylated by deoxycytidine kinase and other nucleotide kinases to the nucleotide form (cytosine arabinoside triphosphate or ara-CTP) to be cytotoxic. Ara-CTP is an effective inhibitor of DNA polymerase. The nucleotide is also incorporated into nuclear DNA and can terminate chain elongation. It is, therefore, S phase (and, hence, cell cycle) specific. *Cytarabine* is not effective when given orally, because of deamination to the noncytotoxic ara-U by cytidine deaminase in the intestinal mucosa and liver. Given IV, it distributes throughout the body but does not penetrate the CNS in sufficient amounts. Therefore, it may also be injected intrathecally for use in meningeal leukemias.

G. Azacitidine

Azacitidine [A-zuh-SITE-i-dine] is a pyrimidine nucleoside analog of cytidine. It is used for the treatment of myelodysplastic syndromes and AML. *Azacitidine* undergoes activation to the nucleotide metabolite azacitidine triphosphate and gets incorporated into DNA and RNA to inhibit gene expression and RNA processing and function. It is S phase cell cycle specific.

H. Gemcitabine

Gemcitabine [jem-SITE-ah-been] is an analog of the nucleoside deoxycytidine. It is used most commonly for pancreatic cancer and non–small cell lung cancer. *Gemcitabine* is a substrate for deoxycytidine kinase, which phosphorylates the drug to 2′,2′-difluorodeoxycytidine triphosphate (Figure 37.13). *Gemcitabine* is administered by IV infusion. It is deaminated to difluorodeoxyuridine, which is not cytotoxic, and is excreted in urine.

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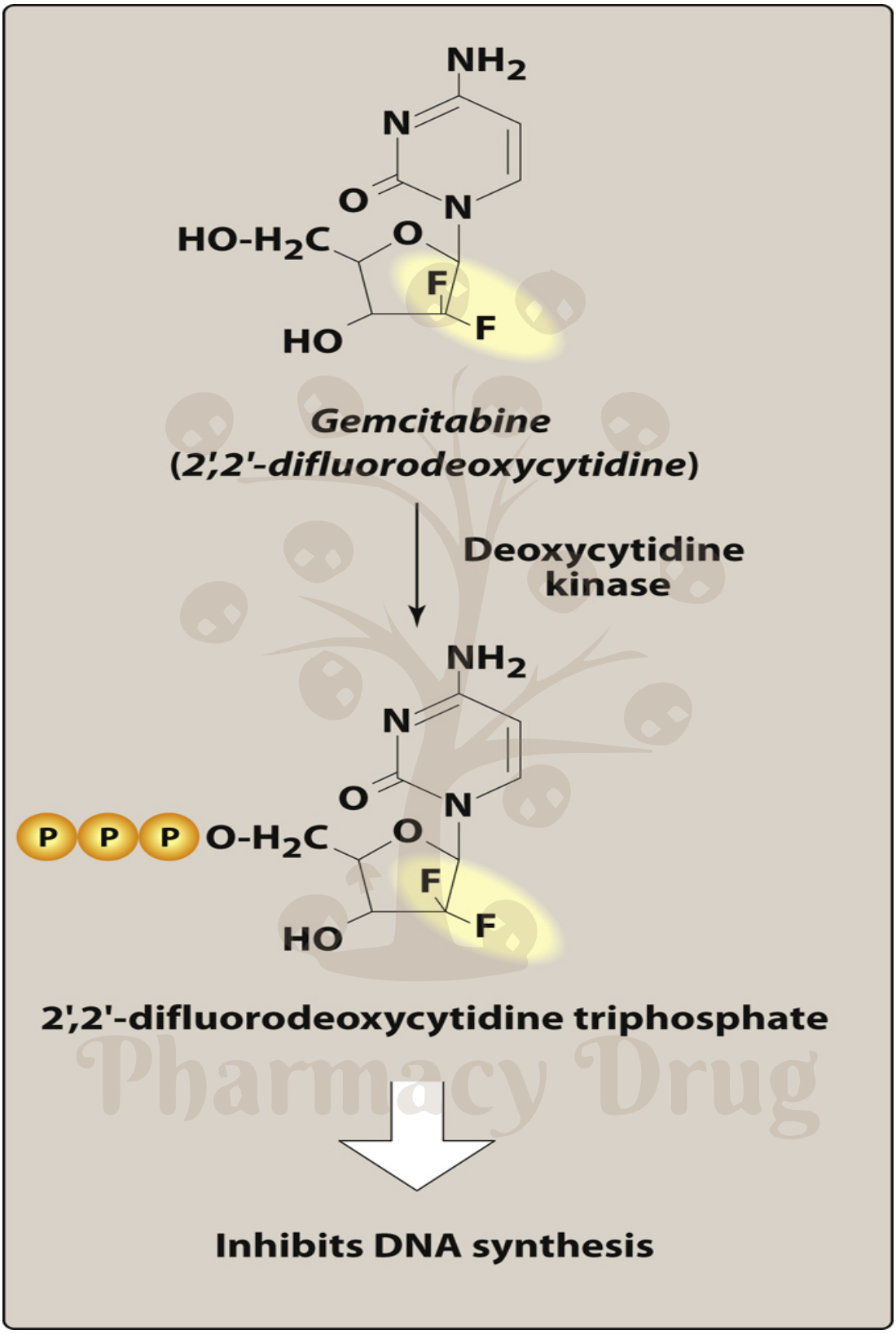

Figure 37.13 Mechanism of action of *gemcitabine*.

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IV. ANTITUMOR ANTIBIOTICS

The antitumor antibiotics (Figure 37.14) are produced from various strains of *Streptomyces* bacteria. They owe their cytotoxic action primarily to their interactions with DNA, leading to disruption of DNA function. In addition to intercalation, anthracyclines also produce cytotoxicity through inhibition of topoisomerase and free radical damage. While the anthracyclines are cell cycle nonspecific, *bleomycin* primarily works in the G_2 phase.

DRUG	ROUTE	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
Doxorubicin	IV	Myelosuppression, N/V/D, mucositis, cardiac toxicity, alopecia, red coloration of urine. Strong vesicants	*Phenytoin, trastuzumab* (cardiotoxicity), *digoxin*	CBC; renal, hepatic function; cardiac function (ECHO or MUGA); adjust in hepatic dysfunction	Cumulative doses >450 mg/m^2 increase risk of cardiotoxicity. Vesicant!
Daunorubicin	IV				Cumulative doses >550 mg/m^2 increase risk of cardiotoxicity. Vesicant!
Liposomal Doxorubicin	IV				Not a substitute for *doxorubicin*, less cardiotoxicity
Epirubicin	IV		*Cimetidine*		Cumulative doses >900 mg/m^2 increase risk of cardiotoxicity. Vesicant! Less N/V
Idarubicin	IV			As with other anthracyclines plus tumor lysis syndrome	Cumulative doses >150 mg/m^2 increase risk of cardiotoxicity. Vesicant!
Bleomycin	IV/SC/IM	Pulmonary fibrosis, alopecia, skin reactions, hyperpigmentation of hands, fever, chills, anaphylaxis	Phenothiazines, *cisplatin* (renal), radiation (pulmonary)	Pulmonary function tests; adjust in renal dysfunction; anaphylaxis	"Bleomycin lung" pulmonary fibrosis can be fatal. Discontinue if any signs of lung dysfunction.

Figure 37.14 Summary of antitumor antibiotics.CBC = complete blood count; D = diarrhea; IM = intramuscular; IV = intravenous; N = nausea; SC = subcutaneous; V = vomiting.

POLE STAR

A. Anthracyclines

Doxorubicin [dox-oh-ROO-bi-sin] and *daunorubicin* [daw-noe-ROO-bi-sin] are classified as anthracycline antibiotics. *Doxorubicin* is the hydroxylated analog of *daunorubicin. Idarubicin* [eye-da-ROO-bi-sin], the 4-demethoxy analog of *daunorubicin, epirubicin* [eh-pee-ROO-bih-sin], and the anthracycline derivative *mitoxantrone* [mye-toe-ZAN-trone] are also available. Therapeutic uses for these agents differ

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despite their structural similarity and apparently similar mechanisms of action. *Doxorubicin* is one of the most important and widely used anticancer drugs. It is used in combination with other agents for treatment of sarcomas and a variety of carcinomas, including breast cancer and many metastatic solid tumors. It is also used for many leukemias and lymphomas. *Daunorubicin* and *idarubicin* are used in the treatment of acute leukemias, and *mitoxantrone* is used in AML and prostate cancer.

1.Mechanism of action: *Doxorubicin* and other anthracyclines induce cytotoxicity through several different mechanisms, including DNA intercalation and inhibition of DNA repair through inhibition of topoisomerase II. This results in blockade of DNA and RNA synthesis and fragmentation of DNA. In addition, free radicals can induce membrane lipid peroxidation, DNA strand scission, and direct oxidation of purine or pyrimidine bases, thiols, and amines (Figure 37.15).

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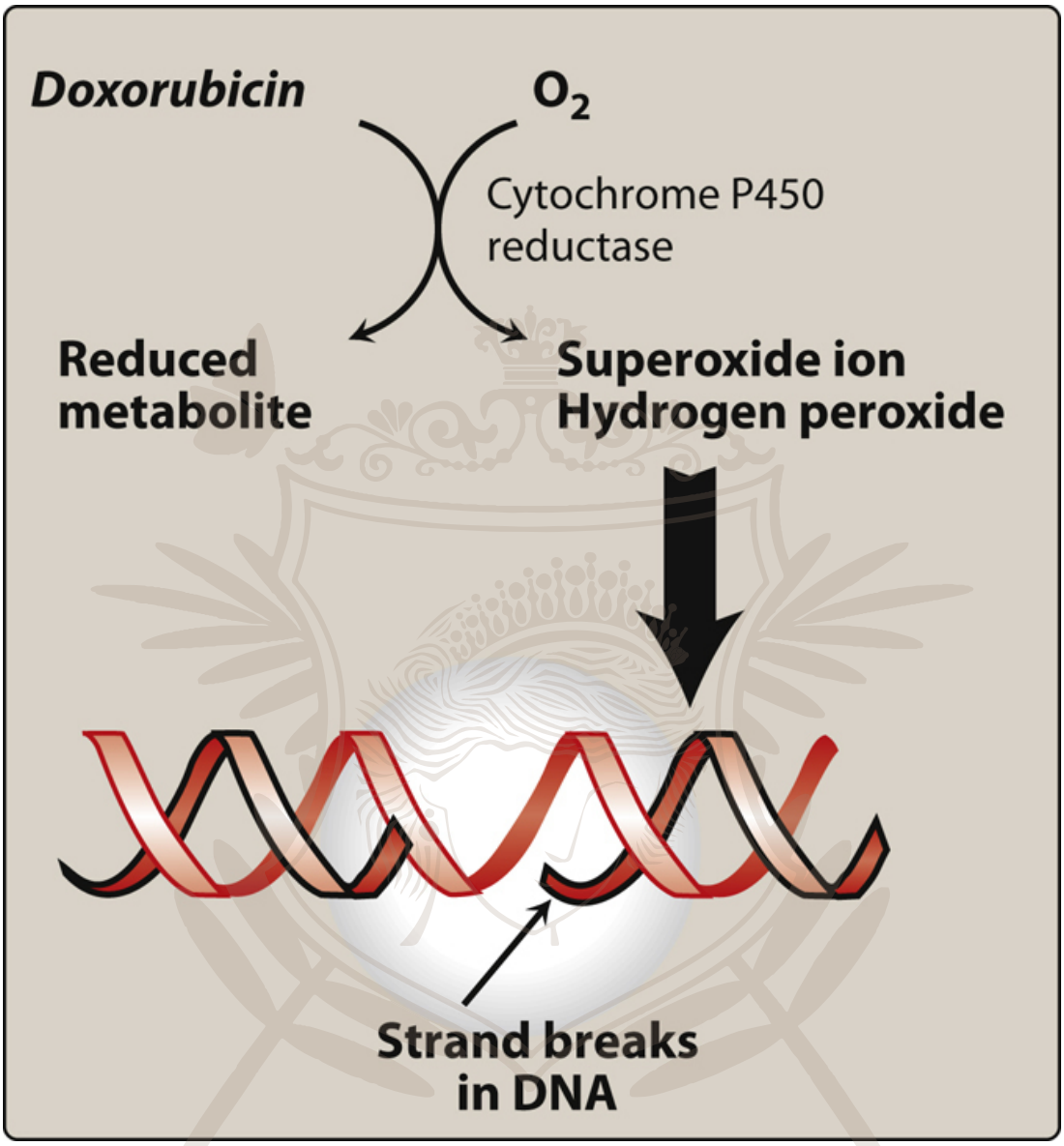

Figure 37.15 *Doxorubicin* interacts with molecular oxygen, producing superoxide ions and hydrogen peroxide, which cause single-strand breaks in DNA.

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2.Pharmacokinetics: These agents must be administered intravenously, because they are inactivated in the GI tract. Extravasation is a serious problem that can lead to tissue necrosis. The anthracycline antibiotics bind to plasma proteins as well as to other tissue components, where they are widely distributed. They do not penetrate the blood–brain barrier or the testes. These

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agents undergo extensive hepatic metabolism, and dosage adjustments are needed in patients with impaired hepatic function. Biliary excretion is the major route of elimination. Because of the dark red color of the anthracycline drugs, the veins may become visible surrounding the site of infusion, and red discoloration of urine may occur.

3.Adverse effects: Irreversible, dose-dependent cardiotoxicity is the most serious adverse reaction, which may lead to left ventricular dysfunction and heart failure. Left ventricular ejection fraction should be monitored closely both during and after treatment. Cardiotoxicity apparently results from the generation of free radicals and lipid peroxidation. Addition of other cardiotoxic agents, such as *trastuzumab,* to protocols with anthracyclines increases the risk of heart failure. There has been some success with the use of liposomal preparations of *doxorubicin* or addition of the iron chelator *dexrazoxane* in protecting against the cardiotoxicity of *doxorubicin*.

B. Bleomycin

Bleomycin [blee-oh-MYE-sin] is a mixture of different copper-chelating glycopeptides that, like the anthracycline antibiotics, cause scission of DNA by an oxidative process. *Bleomycin* is cell cycle specific and causes cells to accumulate in the G_2 phase. It is primarily used in the treatment of testicular cancers and Hodgkin lymphoma.

1.Mechanism of action: A DNA–*bleomycin*–Fe^{2+} complex appears to undergo oxidation to *bleomycin*–Fe^{3+}. The liberated electrons react with oxygen to form superoxide or hydroxyl radicals, which, in turn, attack the phosphodiester bonds of DNA, resulting in strand breakage and chromosomal aberrations (Figure 37.16).

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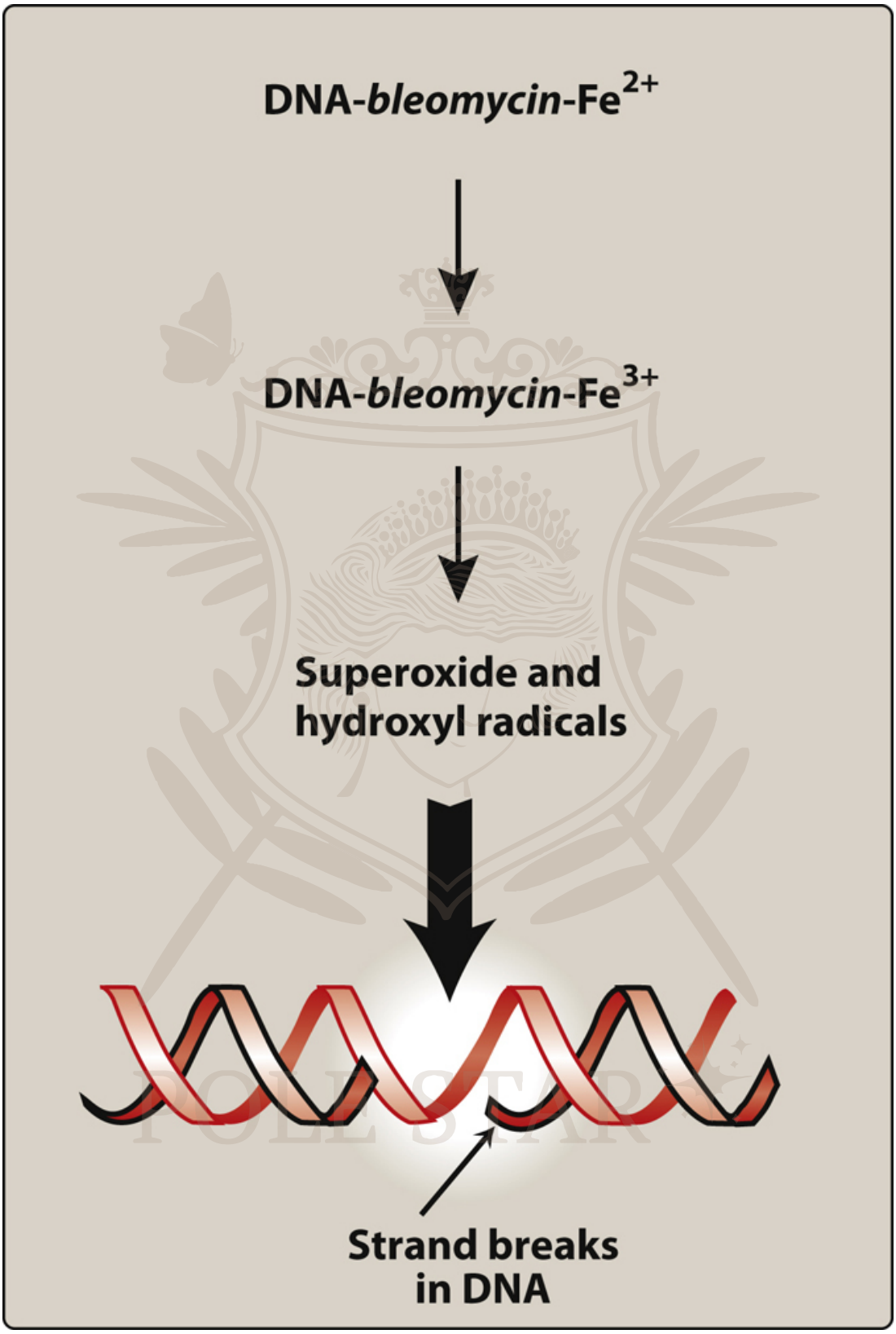

Figure 37.16 *Bleomycin* causes breaks in DNA by an oxidative process.

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2.Pharmacokinetics: *Bleomycin* is administered by a number of routes. The *bleomycin*-inactivating enzyme (a hydrolase) is high in a number of tissues (for example, liver and spleen) but is low in the lung and absent in the skin, accounting for toxicity in those tissues. Most of the parent drug is excreted unchanged in the urine, necessitating dose adjustment in patients with renal failure.

3.Adverse effects: Pulmonary toxicity is the most serious adverse effect, progressing from rales, cough, and infiltrate to potentially fatal fibrosis. The pulmonary fibrosis that is caused by *bleomycin* is often referred as "*bleomycin* lung." Hypertrophic skin changes and hyperpigmentation of the hands are prevalent. *Bleomycin* is unusual in that myelosuppression is rare.

V. ALKYLATING AND ADDUCTING AGENTS

Alkylating agents (Figure 37.17) exert their cytotoxic effects by covalently binding to nucleophilic groups on various cell constituents. Alkylation of DNA is probably the crucial cytotoxic reaction that is lethal to the tumor cells. Alkylating agents do not discriminate between cycling and resting cells, even though they are most toxic for rapidly dividing cells. They are used in combination with other agents to treat a wide variety of lymphatic and solid cancers. In addition to being cytotoxic, all are mutagenic and carcinogenic and can lead to secondary malignancies such as acute leukemia.

Pharmacy Drug

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DRUG	ROUTE	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
Cyclophosphamide	IV/PO	Myelosuppression, hemorrhagic cystitis, N/V/D, alopecia, amenorrhea, secondary malignancies	*Phenobarbital, phenytoin* (P450); *digoxin*, anticoagulants	Urinalysis; CBC; renal, hepatic function	Good hydration to prevent bladder toxicity (*mesna* with high doses)
Ifosfamide	IV	Myelosuppression, hemorrhagic cystitis, N/V, neurotoxicity, alopecia, amenorrhea	*Phenobarbital, phenytoin* (P450); *cimetidine, allopurinol, warfarin*	Urinalysis; neurotoxicity	Use *mesna* and hydration to prevent bladder toxicity
Carmustine (BCNU)	IV	Myelosuppression, N/V, facial flushing, hepatotoxicity, pulmonary toxicity, impotence, infertility	*Cimetidine, amphotericin B, digoxin, phenytoin*	CBC; PFTs; renal, hepatic function	Also available as an implantable wafer (brain)
Lomustine (CCNU)	PO	Myelosuppression, N/V, pulmonary toxicity, impotence, infertility, neurotoxicity	*Cimetidine*, alcohol	CBC; PFTs; renal function	Administer on an empty stomach
Dacarbazine	IV	Myelosuppression, N/V, flu-like syndrome, CNS toxicity, hepatotoxicity, photosensitivity	*Phenytoin, phenobarbital* (P450)	CBC; renal, hepatic function	Vesicant
Temozolomide	IV/PO	N/V, myelosuppression, headache, fatigue, photosensitivity		CBC; renal, hepatic function	Requires Pneumocystis pneumonia prophylaxis
Melphalan	IV/PO	Myelosuppression, N/V/D, mucositis, hypersensitivity (IV)	*Cimetidine*, steroids, *cyclosporine*	CBC; renal, hepatic function	Take on an empty stomach
Chlorambucil	PO	Myelosuppression, skin rash, pulmonary fibrosis (rare), hyperuricemia, seizures	*Phenobarbital, phenytoin* (P450)	CBC; renal, hepatic function; uric acid	Take with food
Busulfan	IV/PO	Myelosuppression, N/V/D, mucositis, skin rash, pulmonary fibrosis, hepatotoxicity	*Acetaminophen, itraconazole, phenytoin*	CBC; pulmonary symptoms; renal, hepatic function	"*Busulfan* lung"

Figure 37.17 Summary of alkylating agents.CBC = complete blood count; CNS = central nervous system; D = diarrhea; IV = intravenous; N = nausea; PFT = pulmonary function test; PO = by mouth; V = vomiting.

A. Cyclophosphamide and ifosfamide

These drugs are very closely related mustard agents that share most of the same primary mechanisms and toxicities. They are cytotoxic only after generation of their alkylating species, which are produced through hydroxylation by cytochrome P450 (CYP450). These agents have a broad clinical spectrum and are used as single agents or in combinations in the treatment of a wide variety of neoplastic diseases, such as non-Hodgkin lymphoma, sarcoma, and breast cancer.

1.Mechanism of action: *Cyclophosphamide* [sye-kloe-FOSS-fah-mide] is a commonly used alkylating agent. Both *cyclophosphamide* and *ifosfamide* [eye-FOSS-fah-mide] are first biotransformed to hydroxylated intermediates primarily in the liver by the CYP450 system (Figure 37.18). The hydroxylated intermediates then undergo metabolism to form the active compounds, phosphoramide mustard and acrolein. Reaction of the

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phosphoramide mustard with DNA is considered to be the cytotoxic step.

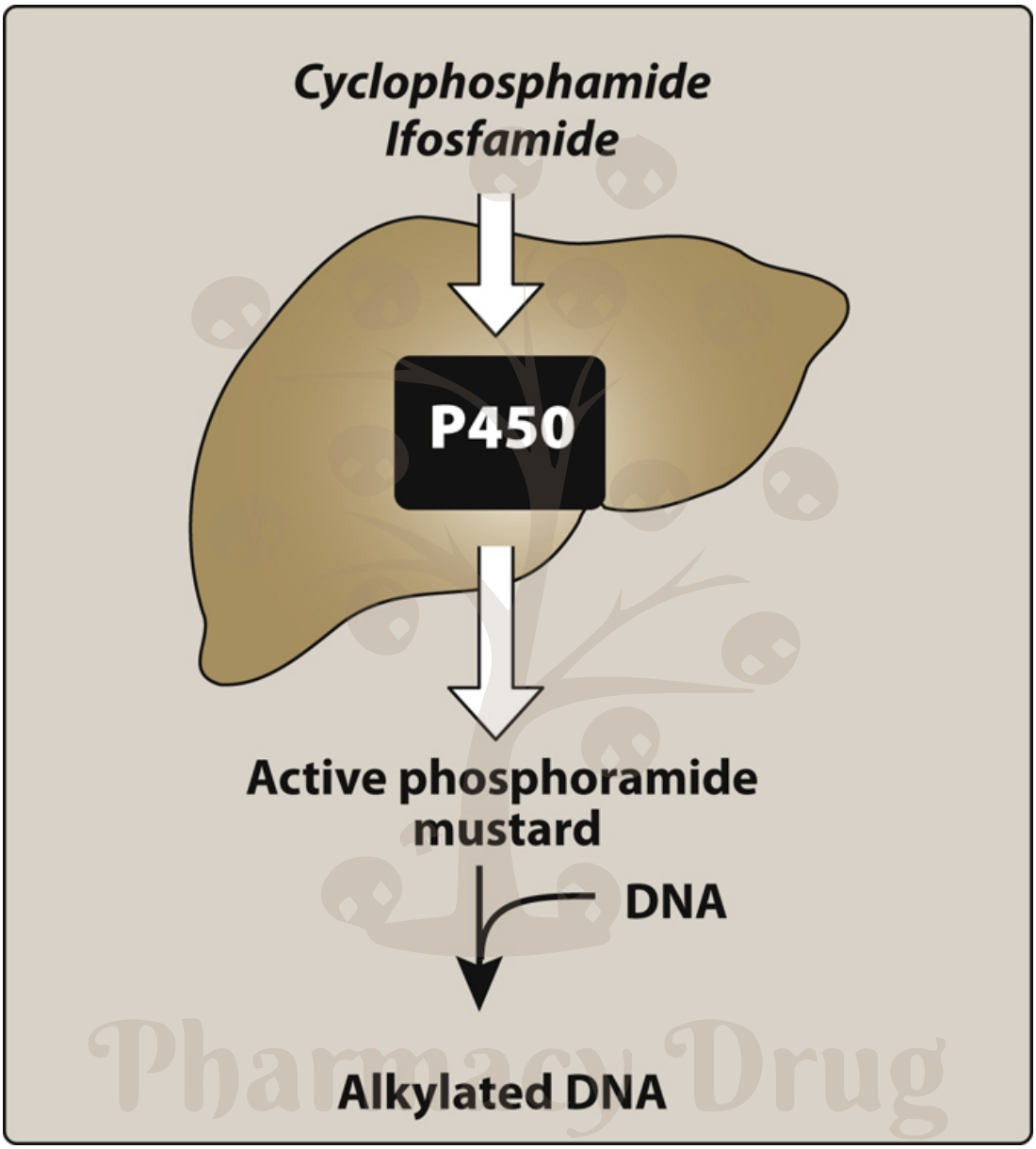

Figure 37.18 Activation of *cyclophosphamide* and *ifosfamide* by hepatic cytochrome P450.

2.Pharmacokinetics: *Cyclophosphamide* is available in oral and IV preparations, whereas *ifosfamide* is IV only.

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Cyclophosphamide is metabolized in the liver to active and inactive metabolites, and minimal amounts are excreted in the urine as unchanged drug. *Ifosfamide* is metabolized primarily by CYP3A4 and CYP2B6 isoenzymes. It is mainly renally excreted.

3.Adverse effects: A unique toxicity of both drugs is hemorrhagic cystitis, an inflammation of the bladder that can lead to symptoms such as dysuria, hematuria, and hemorrhage. Bladder toxicity has been attributed to acrolein in the urine in the case of *cyclophosphamide* and to acrolein and additional toxic metabolites of *ifosfamide.* Adequate hydration as well as IV injection of *mesna* (sodium 2-mercaptoethane sulfonate), which neutralizes the toxic metabolites, can prevent this problem. Neurotoxicity has been reported in patients on high-dose *ifosfamide*, probably due to the metabolite chloroacetaldehyde.

B. Nitrosoureas

Carmustine [KAR-mus-teen, BCNU] and *lomustine* [LOE-mus-teen, CCNU] are closely related nitrosoureas. Because of their ability to penetrate the CNS, the nitrosoureas are primarily employed in the treatment of brain tumors.

1.Mechanism of action: The nitrosoureas exert cytotoxic effects by DNA alkylation that inhibits replication and, eventually, RNA and protein synthesis. Although they alkylate DNA in resting cells, cytotoxicity is expressed primarily in cells that are actively dividing. Therefore, nondividing cells can escape death if DNA repair occurs. Nitrosoureas also inhibit several key enzymatic processes by carbamoylation of amino acids in proteins in the targeted cells.

2.Pharmacokinetics: *Carmustine* is administered IV and as chemotherapy wafer implants, whereas *lomustine* is given orally. Because of their lipophilicity, these agents distribute widely in the body and readily penetrate the CNS. The drugs undergo extensive metabolism. *Lomustine* is metabolized to active products. The kidney is the major excretory route for the nitrosoureas (Figure 37.19).

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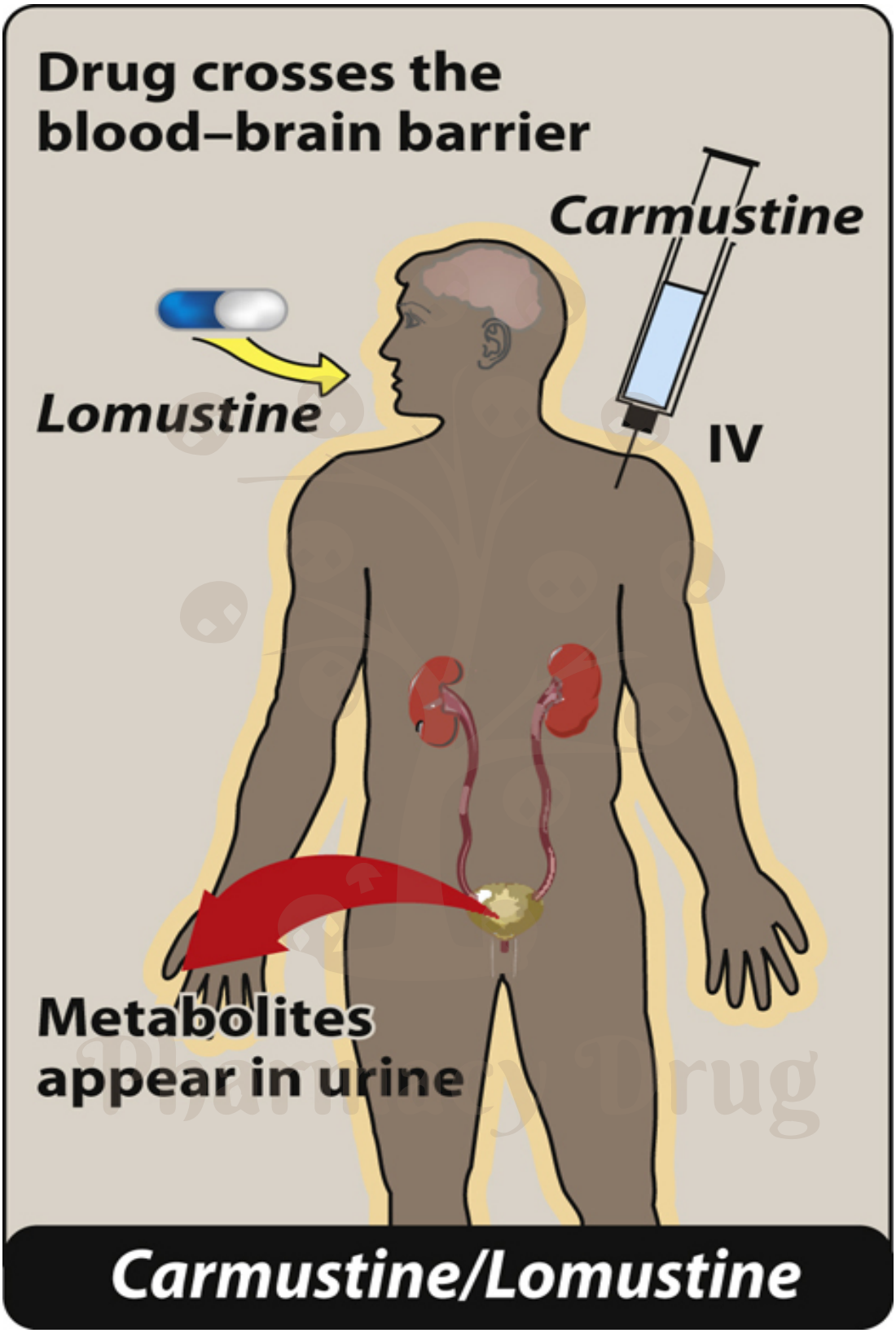

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Figure 37.19 Administration and fate of *carmustine/lomustine*.IV = intravenous.

C. Dacarbazine and temozolomide

Dacarbazine [dah-KAR-bah-zeen] is an alkylating agent that must undergo biotransformation by CYP450 enzymes to an active metabolite, methyltriazenoimidazole carboxamide (MTIC). The metabolite is responsible for the alkylating activity of this agent by forming methyl carbonium ions that attack the nucleophilic groups in the DNA molecule. The cytotoxic action of *dacarbazine* has been attributed to the ability of its metabolite to methylate DNA on the O-6 and N-7 positions of guanine. *Dacarbazine* has found use in the treatment of melanoma and Hodgkin lymphoma.

Temozolomide [te-moe-ZOE-loe-mide] is related to *dacarbazine*, because both must undergo biotransformation to an active metabolite, MTIC, which is likely responsible for the methylation of DNA on the O-6 and N-7 positions of guanine. Unlike *dacarbazine*, *temozolomide* does not require the CYP450 system for metabolic transformation to MTIC, and it undergoes chemical transformation at normal physiological pH. *Temozolomide* also inhibits the repair enzyme, O-6-guanine-DNA alkyltransferase. *Temozolomide* differs from *dacarbazine* in that it crosses the blood–brain barrier and, therefore, is used in the treatment of brain tumors such as glioblastomas and astrocytomas. It is also used in metastatic melanoma. *Temozolomide* is administered intravenously or orally and has excellent bioavailability after oral administration. The parent drug and metabolites are excreted in urine (Figure 37.20).

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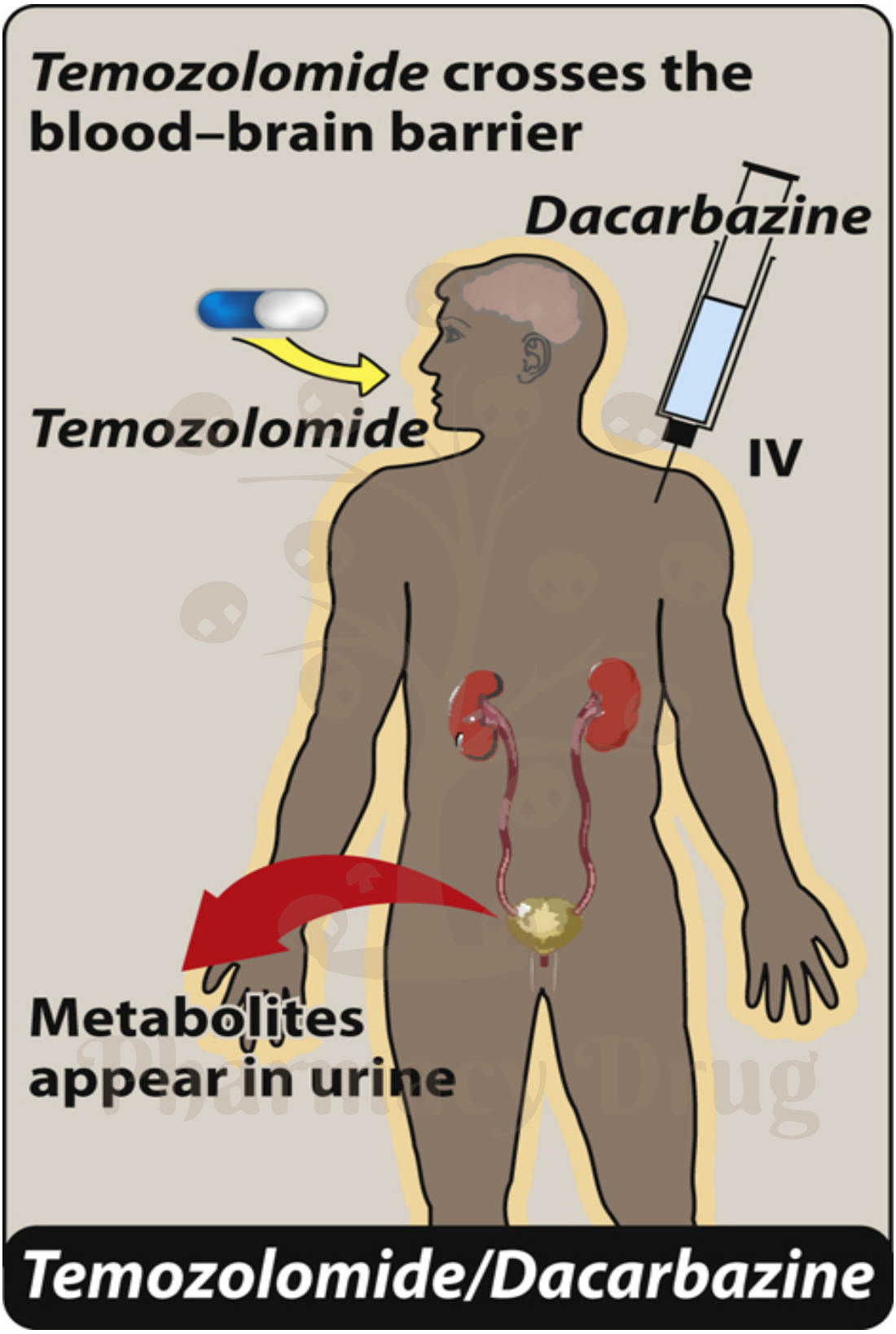

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Figure 37.20 Administration and fate of *temozolomide* and *dacarbazine*.IV = intravenous.

D. Platinum coordination complexes

Cisplatin [SIS-pla-tin] was the first member of the platinum coordination complex class of anticancer drugs, but because of severe toxicity, *carboplatin* [KAR-boe-pla-tin] was developed. The potency, pharmacokinetics, patterns of distribution, and dose-limiting toxicities differ significantly (Figure 37.21) between these drugs. *Cisplatin* has synergistic cytotoxicity with radiation and other chemotherapeutic agents. It has found wide application in the treatment of solid tumors, such as metastatic testicular carcinoma in combination with *vinblastine* and *bleomycin*, ovarian carcinoma in combination with *cyclophosphamide*, or alone for bladder carcinoma. *Carboplatin* is used when patients cannot be vigorously hydrated, as is required for *cisplatin* treatment, or if they suffer from kidney dysfunction or are prone to neuro- or ototoxicity. *Oxaliplatin* [ox-AL-ih-pla-tin] is a closely related analog of *carboplatin* used in the setting of colorectal cancer.

DRUG	ROUTE	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
Cisplatin	IV, IP, IA	Neurotoxicity, myelosuppression, ototoxicity, N, V, electrolyte wasting, infusion reaction, nephrotoxicity	Anticonvulsants	CBC, CMP, electrolytes, hearing	Aggressive pre- and posthydration required, high incidence of N/V
Carboplatin	IV, IP, IA	Myelosuppression, N, V, infusion reaction	Aminoglycosides	CBC	Dose calculated using AUC
Oxaliplatin	IV	Neurotoxicity, N, V, infusion reaction, hepatotoxicity, myelosuppression	*Warfarin*	CBC, neurologic function, hepatic function	Cold-related and cumulative peripheral neuropathy

Figure 37.21 Summary of platinum coordination complexes.AUC = area under the curve; CBC = complete blood count; CMP = complete metabolic panel; IA = intra-arterially; IP = intraperitoneally; IV = intravenous; N = nausea; V = vomiting.

1.Mechanism of action: The mechanism of action for these agents is similar to that of the alkylating agents. In the high-chloride milieu of the plasma, *cisplatin* persists as the neutral species, which enters the cell and loses chloride in the low-chloride milieu. It then binds to guanine in DNA, forming inter- and

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intrastrand cross-links. The resulting cytotoxic lesion inhibits both polymerases for DNA replication and RNA synthesis. Cytotoxicity can occur at any stage of the cell cycle, but cells are most vulnerable to the actions of these drugs in the G_1 and S phases.

2.Pharmacokinetics: These agents are administered via IV infusion. *Cisplatin* and *carboplatin* can also be given intraperitoneally for ovarian cancer and intra-arterially to perfuse other organs. The highest concentrations of the drugs are found in the liver, kidney, and intestinal, testicular, and ovarian cells, but little penetrates into the cerebrospinal fluid (CSF). The renal route is the main pathway of excretion.

3.Adverse effects: Severe nausea and vomiting occurs in most patients after administration of *cisplatin* and may continue for as long as 5 days. Premedication with antiemetic agents is required. The major limiting toxicity is dose-related nephrotoxicity, involving the distal convoluted tubule and collecting ducts. This can be prevented by aggressive hydration. Other toxicities include ototoxicity with high-frequency hearing loss and tinnitus. Unlike *cisplatin*, *carboplatin* causes only mild nausea and vomiting, and it is rarely nephro-, neuro-, or ototoxic. The dose-limiting toxicity is myelosuppression. *Oxaliplatin* has a distinct adverse effect of cold-induced peripheral neuropathy that usually resolves within 72 hours of administration. It also causes myelosuppression and cumulative peripheral neuropathy. Hepatotoxicity has also been reported. These agents may cause hypersensitivity reactions ranging from skin rashes to anaphylaxis.

E. Other alkylating agents

Mechlorethamine [mek-lor-ETH-ah-meen] was developed as a nitrogen mustard following World War I. Its ability to cause lymphocytopenia led to its role as the first alkylating agent developed for use in humans, and the topical gel is used in the treatment of cutaneous T-cell lymphoma today. *Melphalan* [MEL-fah-lan], a phenylalanine derivative of nitrogen mustard, is used in the treatment of multiple myeloma and ovarian cancer. This alkylating agent can be given by IV infusion. It can also be administered orally, although the

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plasma concentration differs from patient to patient due to variation in intestinal absorption and metabolism. The dose of *melphalan* is carefully adjusted by monitoring platelet and white blood cell counts. *Chlorambucil* [clor-AM-byoo-sil] is another alkylating agent that is used in the treatment of lymphomas and chronic lymphocytic leukemia. *Busulfan* [byoo-SUL-fan] is an alkylating agent that is effective against chronic myelogenous leukemia. This agent can cause pulmonary fibrosis ("*busulfan* lung"). Like other alkylating agents, all of these agents can promote the development of leukemia and may lead to a secondary leukemia.

VI. MICROTUBULE INHIBITORS

The mitotic spindle is part of a larger, intracellular skeleton (cytoskeleton) that is essential for the movements of structures occurring in the cytoplasm of all eukaryotic cells. It consists of chromatin plus a system of microtubules composed of the protein tubulin. The mitotic spindle is essential for the equal partitioning of DNA into the two daughter cells that are formed when a eukaryotic cell divides. Several plant-derived substances used as anticancer drugs disrupt this process by affecting the equilibrium between the polymerized and depolymerized forms of the microtubules, thereby causing cytotoxicity. The microtubule inhibitors are summarized in Figure 37.22.

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DRUG	ROUTE	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
Vincristine	IV	Neurotoxicity, constipation	*Clarithromycin, azole antifungals, phenytoin, carbamazepine, ritonavir* (CYP3A4)	CBC, hepatic function, peripheral neuropathy	Vesicants; IT administration may result in death
Vinblastine	IV	Myelosuppression, neurotoxicity		CBC, hepatic function	
Vinorelbine	IV	Granulocytopenia			
Paclitaxel	IV	Neutropenia, neurotoxicity, alopecia, N, V	*Gemfibrozil* (CYP2C8); NSAIDs (risk of bleeding)	CBC, hepatic function, peripheral neuropathy	Hypersensitivity reactions (dyspnea, urticaria, hypotension); require premedications
Docetaxel	IV	Neutropenia, neurotoxicity, fluid retention, alopecia, N, V, D	*Clarithromycin, azole antifungals, phenytoin, carbamazepine, ritonavir* (CYP3A4); NSAIDs (risk of bleeding)		

Figure 37.22 Summary of microtubule inhibitors.CBC = complete blood count; D = diarrhea; IT = intrathecal; IV = intravenous; N = nausea; NSAIDs = nonsteroidal anti-inflammatory drugs; V = vomiting.

A. Vinca alkaloids

The vinca alkaloids, *vincristine* [vin-KRIS-teen], *vinblastine* [vin-BLAS-teen], and *vinorelbine* [vye-NOR-el-been], are structurally related compounds derived from the periwinkle plant. Although the vinca alkaloids are structurally similar, their therapeutic indications are different. They are generally administered in combination with other drugs. *Vincristine* is used in the treatment of acute lymphoblastic leukemia in children, Wilms tumor, rhabdosarcoma, Ewing soft tissue sarcoma, and Hodgkin and non-Hodgkin lymphomas, as well as some other rapidly proliferating neoplasms. [Note: *Vincristine* (former trade name, *Oncovin*) is the "O" in the R-CHOP regimen for lymphoma. Due to relatively mild myelosuppressive activity, it is also used in a number of other protocols.] *Vinblastine* is administered with *bleomycin* and *cisplatin* for the treatment of metastatic testicular carcinoma. It is also used in the treatment of systemic Hodgkin and non-Hodgkin lymphomas as well as Kaposi sarcoma. *Vinorelbine* is beneficial in the treatment of breast cancer and advanced non–small cell lung cancer, either as a single agent or with *cisplatin*.

1.Mechanism of action: These agents are cell cycle specific and phase specific, because they block mitosis in metaphase (M phase). Their binding to the microtubular protein, tubulin, blocks the ability of tubulin to polymerize to form microtubules. Instead, paracrystalline aggregates consisting of tubulin dimers and the

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alkaloid drug are formed. The resulting dysfunctional spindle apparatus, frozen in metaphase, prevents chromosomal segregation and cell proliferation (Figure 37.23).

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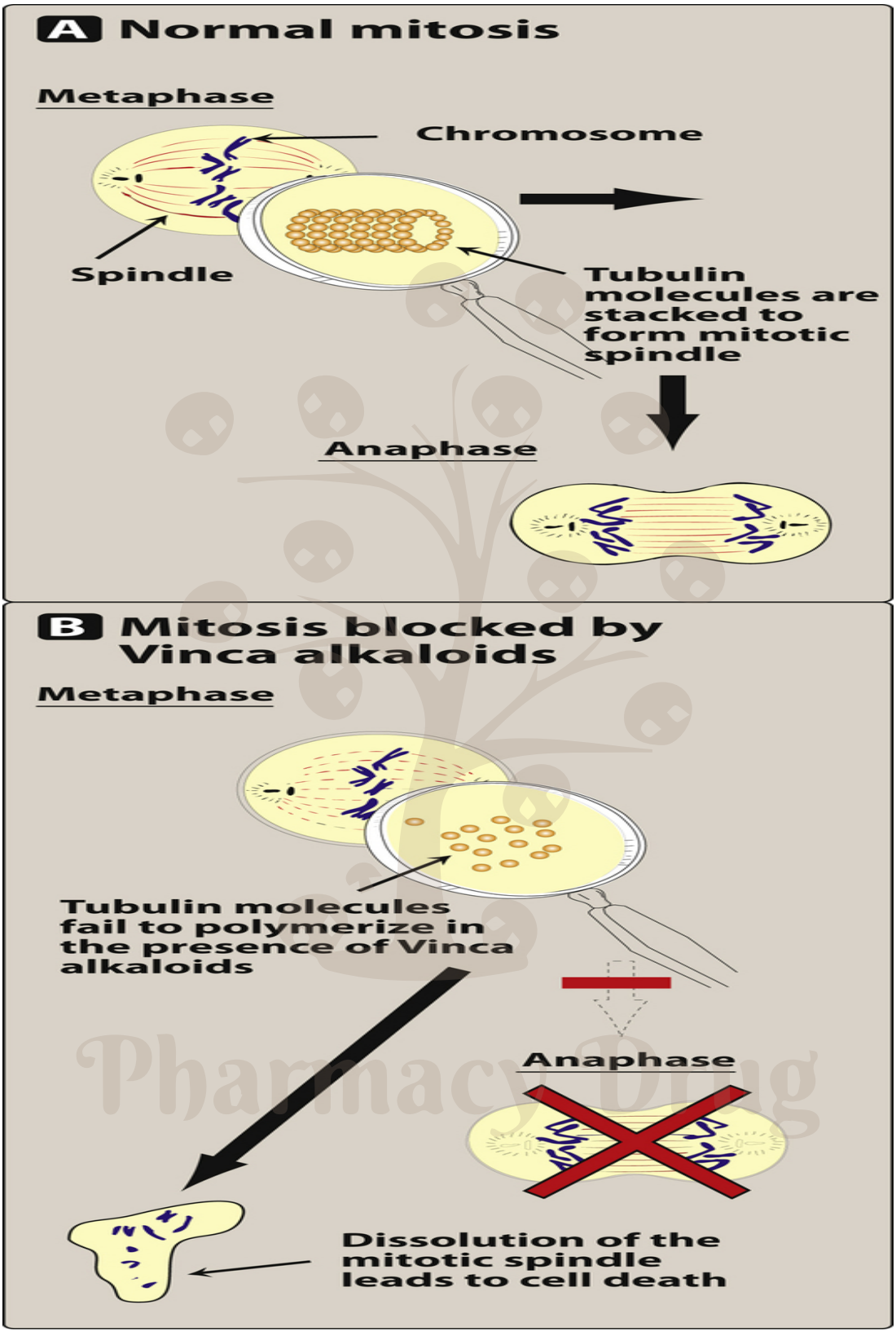

Figure 37.23 Mechanism of action of the microtubule inhibitors.

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2.Pharmacokinetics: IV injection of these agents leads to rapid cytotoxic effects and cell destruction. This, in turn, can cause hyperuricemia due to the oxidation of purines that are released from fragmenting DNA molecules. The vinca alkaloids are concentrated and metabolized in the liver by the CYP450 pathway and eliminated in bile and feces. Dosage adjustment is required in patients with impaired hepatic function or biliary obstruction.

3.Adverse effects: These agents are associated with phlebitis or cellulitis if extravasation occurs during injection, as well as nausea, vomiting, diarrhea, and alopecia. *Vinblastine* and *vinorelbine* are potent myelosuppressant agents, whereas peripheral neuropathy (paresthesias, loss of reflexes, foot drop, and ataxia) and constipation are more common with *vincristine.* These agents should not be administered intrathecally. This potential drug error can result in death, and special precautions should be in place for administration.

B. Taxanes

Paclitaxel [PAK-li-tax-el] was the first member of the taxane family to be used in cancer chemotherapy. Semisynthetic *paclitaxel* and *albumin-bound paclitaxel* are also available. Substitution of a side chain resulted in *docetaxel* [doe-see-TAX-el], which is the more potent of the two drugs. *Paclitaxel* has good activity against advanced ovarian cancer and metastatic breast cancer, as well as non–small cell lung cancer when administered with *cisplatin. Docetaxel* is commonly used in prostate, breast, GI, and non–small cell lung cancers.

1.Mechanism of action: Both drugs are active in the G_2/M phase of the cell cycle, but unlike the vinca alkaloids, they promote polymerization and stabilization of the polymer rather than disassembly, leading to the accumulation of microtubules (Figure 37.24). The microtubules formed are overly stable and nonfunctional, and chromosome desegregation does not occur. This results in cell death.

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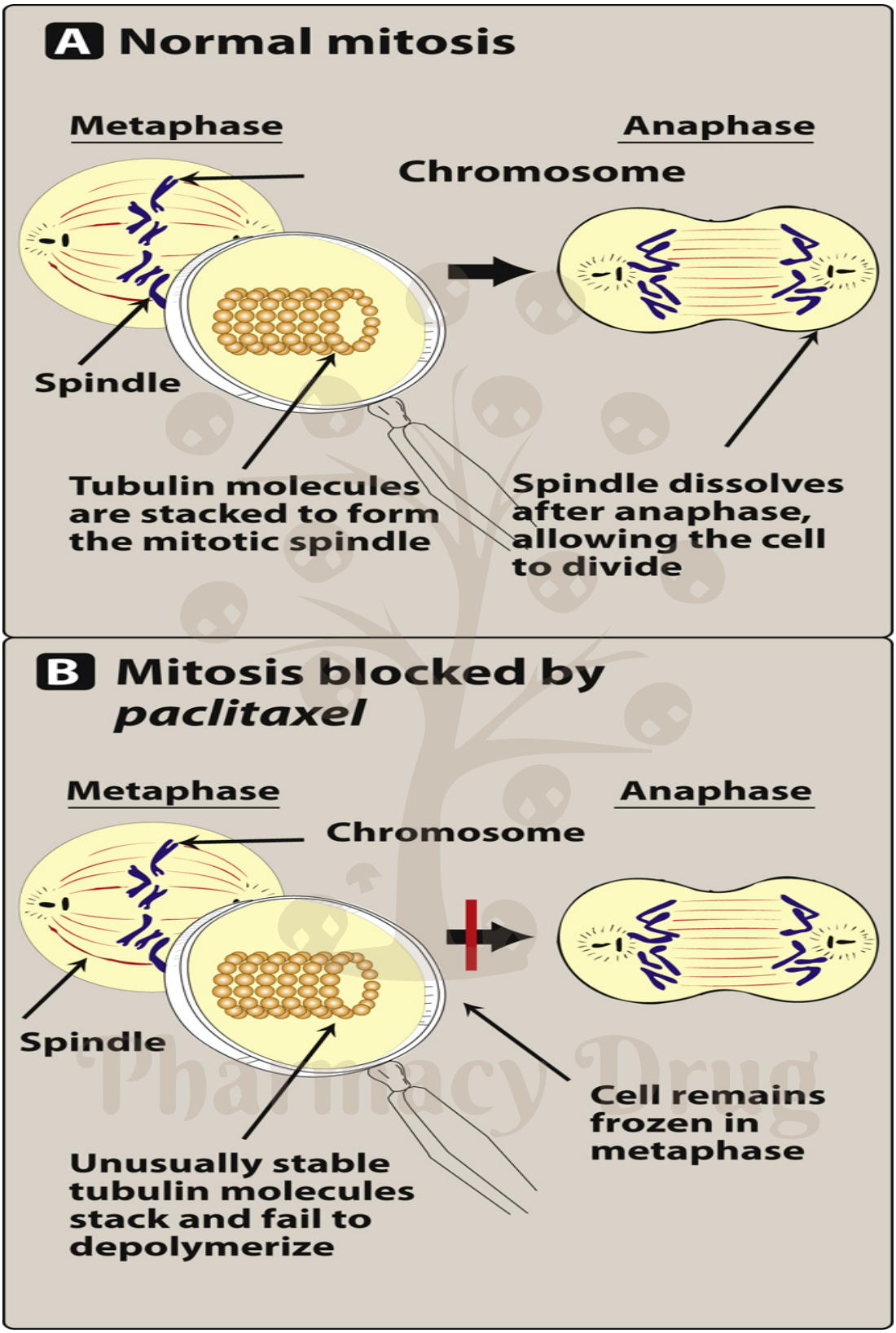

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Figure 37.24 *Paclitaxel* stabilizes microtubules, rendering them nonfunctional.

2.Pharmacokinetics: These agents undergo hepatic metabolism by the CYP450 system and are excreted via the biliary system. Dosages should be reduced in patients with hepatic dysfunction.

3.Adverse effects: The dose-limiting toxicities of *paclitaxel* and *docetaxel* are neutropenia and leukopenia. Peripheral neuropathy is also a common adverse effect with the taxanes. Because of serious hypersensitivity reactions (including dyspnea, urticaria, and hypotension), patients who are treated with *paclitaxel* should be premedicated with *dexamethasone* and *diphenhydramine*, as well as with an H_2 receptor antagonist. *Docetaxel* can lead to severe fluid retention, such as peripheral edema or pleural or pericardial effusions. For this reason, patients being treated with *docetaxel* should be pretreated with *dexamethasone*.

VII. STEROID HORMONES AND THEIR ANTAGONISTS

Tumors that are sensitive to steroid hormones may be either (1) hormone responsive, in which the tumor regresses following treatment with a specific hormone; or (2) hormone dependent, in which removal of a hormonal stimulus causes tumor regression; or (3) both. Removal of hormonal stimuli from hormone-dependent tumors can be accomplished by surgery (for example, in the case of orchiectomy—surgical removal of one or both testes—for patients with advanced prostate cancer) or by drugs (for example, breast cancer treatment with the antiestrogen *tamoxifen* prevents estrogen stimulation of breast cancer cells; Figure 37.25). For a steroid hormone to influence a cell, that cell must have intracellular (cytosolic) receptors that are specific for that hormone (Figure 37.26A).

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DRUG	ROUTE	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
Tamoxifen	PO	Hot flashes, N, V, vaginal bleeding, hypercalcemia, thromboembolism	*Warfarin, rifampin*	Vaginal bleeding, new breast lumps	May cause endometrial cancer
Anastrozole ***Letrozole***	PO	Hot flashes, N, joint pain, ischemic cardiovascular events, osteoporosis	Estrogen-containing products	Hepatic function, bone mineral density monitoring, cholesterol monitoring	Contraindicated in premenopausal or pregnant women
Leuprolide ***Goserelin*** ***Triptorelin***	Depot, SC IM	Tumor flare, hot flashes, asthenia, gynecomastia		Bone mineral density monitoring, serum testosterone, PSA	
Apalutamide ***Bicalutamide*** ***Darolutamide*** ***Flutamide*** ***Nilutamide***	PO	Hot flashes, N, gynecomastia, pain, constipation	*Warfarin*	Hepatic function, PSA	Combined with LHRH agonists or surgical castration

Figure 37.25 Summary of selected steroid hormones and their antagonists.IM = intramuscular; LHRH = luteinizing hormone–releasing hormone; N = nausea; PO = oral administration; PSA = prostate-specific antigen; SC = subcutaneous; V = vomiting.

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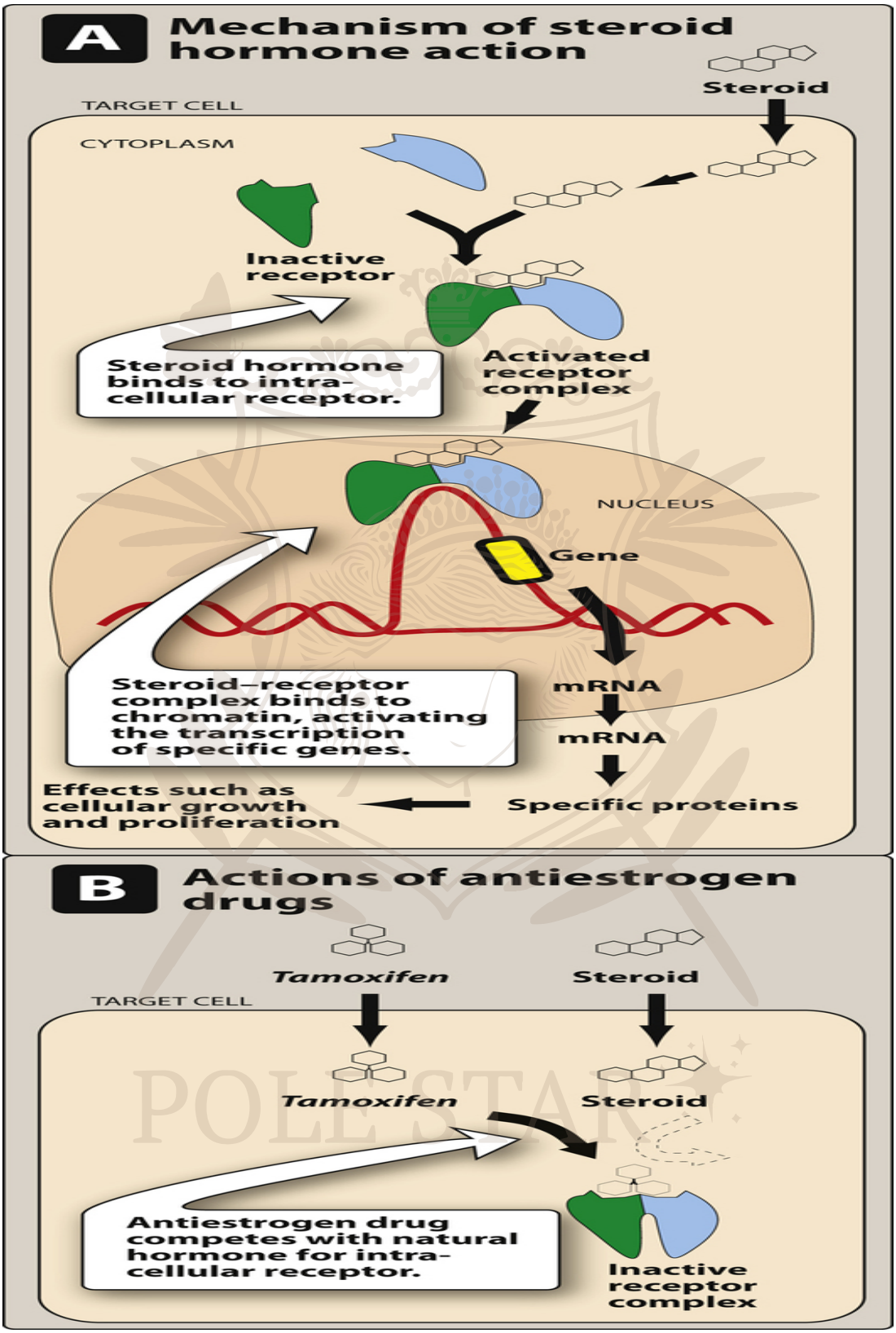
A
Mechanism of steroid hormone action
Steroid
TARGET CELL
CYTOPLASM
Inactive receptor
Steroid hormone binds to intra-cellular receptor.
Activated receptor complex
NUCLEUS
Gene
Steroid–receptor complex binds to chromatin, activating the transcription of specific genes.
mRNA
mRNA
Specific proteins
Effects such as cellular growth and proliferation
B
Actions of antiestrogen drugs
Tamoxifen
Steroid
TARGET CELL
Tamoxifen
Steroid
Antiestrogen drug competes with natural hormone for intra-cellular receptor.
Inactive receptor complex

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Figure 37.26 Action of steroid hormones and antiestrogen agents.mRNA = messenger RNA.

A. Selective estrogen receptor modulators

Tamoxifen [tah-MOX-ih-fen] is a selective estrogen receptor modulator (SERM). It is an estrogen antagonist in breast tissue and an agonist in other tissues, such as bone and the endometrium. *Tamoxifen* is used for first-line therapy in the treatment of estrogen receptor–positive breast cancer. It is also used for prevention of breast cancer in high-risk women. *Raloxifene* [ral-OKS-i-feen] is a SERM that blocks estrogen effects in the uterine and breast tissues, while promoting effects in the bone to inhibit resorption. This agent reduces the risk of estrogen receptor–positive invasive breast cancer in postmenopausal women.

1.Mechanism of action: *Tamoxifen* competes with estrogen for binding to estrogen receptors in the breast tissue and inhibits estrogen-induced growth of breast cancer (Figure 37.26B). *Raloxifene* also blocks the effects of estrogen in breast tissue. The mechanism of the different effects of SERMs in various tissues is not well understood, although it may be due to differences in coregulator expression or recruitment, or different dimer combinations of estrogen receptors.

2.Pharmacokinetics: *Tamoxifen* is effective after oral administration; however, it is partially metabolized by the liver and some metabolites possess more potent SERM activity than *tamoxifen.* Unchanged drug and metabolites are excreted predominantly through the bile into the feces. *Tamoxifen* is an inhibitor of CYP3A4 and P-glycoprotein.

3.Adverse effects: Adverse effects caused by *tamoxifen* include hot flashes, nausea, vomiting, skin rash, and vaginal bleeding and discharge (due to estrogenic activity of the drug and some of its metabolites in the endometrial tissue). *Tamoxifen* has the potential to cause endometrial cancer. Other toxicities include thromboembolism and effects on vision. Since *raloxifene* does not have estrogenic activity in the endometrium, it does not increase

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the risk of endometrial cancer. It is also associated with less vaginal discharge and severe hot flashes compared with *tamoxifen*.

B. Fulvestrant

Fulvestrant [fool-VES-trant] is an estrogen receptor antagonist that is given via intramuscular injection to patients with hormone receptor–positive metastatic breast cancer. This agent binds to and causes estrogen receptor downregulation on tumors and other targets. Adverse effects include hot flashes, injection site reactions, and the potential for increased liver enzymes.

C. Aromatase inhibitors

The aromatase reaction is responsible for extra-adrenal synthesis of estrogen from androstenedione, which takes place in liver, fat, muscle, skin, and breast tissues, including breast malignancies. Peripheral aromatization is an important source of estrogen in postmenopausal women. Aromatase inhibitors decrease the production of estrogen in these women.

1.Anastrozole and letrozole: *Anastrozole* [an-AS-troe-zole] and *letrozole* [LE-troe-zole] are nonsteroidal aromatase inhibitors. These agents are considered first-line drugs for the treatment of breast cancer in postmenopausal women. They are orally active and cause almost a total suppression of estrogen synthesis in postmenopausal women where extra-adrenal estrogen synthesis accounts for the vast majority of circulating estrogen. [Note: *Letrozole* is also used in the management of infertility for women who are anovulatory or experience irregular ovulation.] *Anastrozole* and *letrozole* do not predispose patients to endometrial cancer. Both drugs are extensively metabolized in the liver, and metabolites and parent drug are excreted primarily in the urine.

2.Exemestane: A steroidal, irreversible inhibitor of aromatase, *exemestane* [ex-uh-MES-tane], is well absorbed after oral administration and widely distributed. This agent is used in the treatment of breast cancer in postmenopausal women who have already been treated with *tamoxifen* or other therapies. Hepatic

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metabolism occurs via the CYP3A4 isoenzyme. Because the metabolites are excreted in urine, dosage of the drug must be adjusted in patients with renal failure. Major toxicities are nausea, fatigue, and hot flashes. Alopecia and dermatitis have also been noted.

D. Gonadotropin-releasing hormone agonists

Gonadotropin-releasing hormone (GnRH) is normally secreted by the hypothalamus and stimulates the anterior pituitary to secrete the gonadotropic hormones: (1) luteinizing hormone (LH), the primary stimulus for the secretion of testosterone by the testes and (2) follicle-stimulating hormone (FSH), which stimulates the secretion of estrogen. *Leuprolide* [loo-PROE-lide], *goserelin* [GOE-se-rel-in], and *triptorelin* [TRIP-to-rel-in] are synthetic analogs of GnRH. As GnRH analogs, they occupy the GnRH receptor in the pituitary, which leads to its desensitization and, consequently, inhibition of release of FSH and LH. Thus, both androgen and estrogen syntheses are reduced (Figure 37.27). These drugs can be used in premenopausal breast cancer and prostate cancer, as well as other indications like endometriosis and uterine fibroids. The response to *leuprolide* in prostatic cancer is equivalent to that of an orchiectomy with regression of tumor and relief of bone pain. *Leuprolide* is available as (1) a subcutaneous daily injection, (2) a subcutaneous depot injection, or (3) an intramuscular depot injection to treat metastatic carcinoma of the prostate. *Goserelin acetate* is a subcutaneous implant, and *triptorelin pamoate* is injected intramuscularly. Levels of testosterone in males with prostate cancer and estrogen in females with breast cancer may initially rise due to receptor activation prior to desensitization. This transient increase leads to the potential for a tumor flare and worsening of disease signs and symptoms during the first few weeks of therapy. Other adverse effects may include sexual dysfunction, hot flashes, and decreased bone mineral density.

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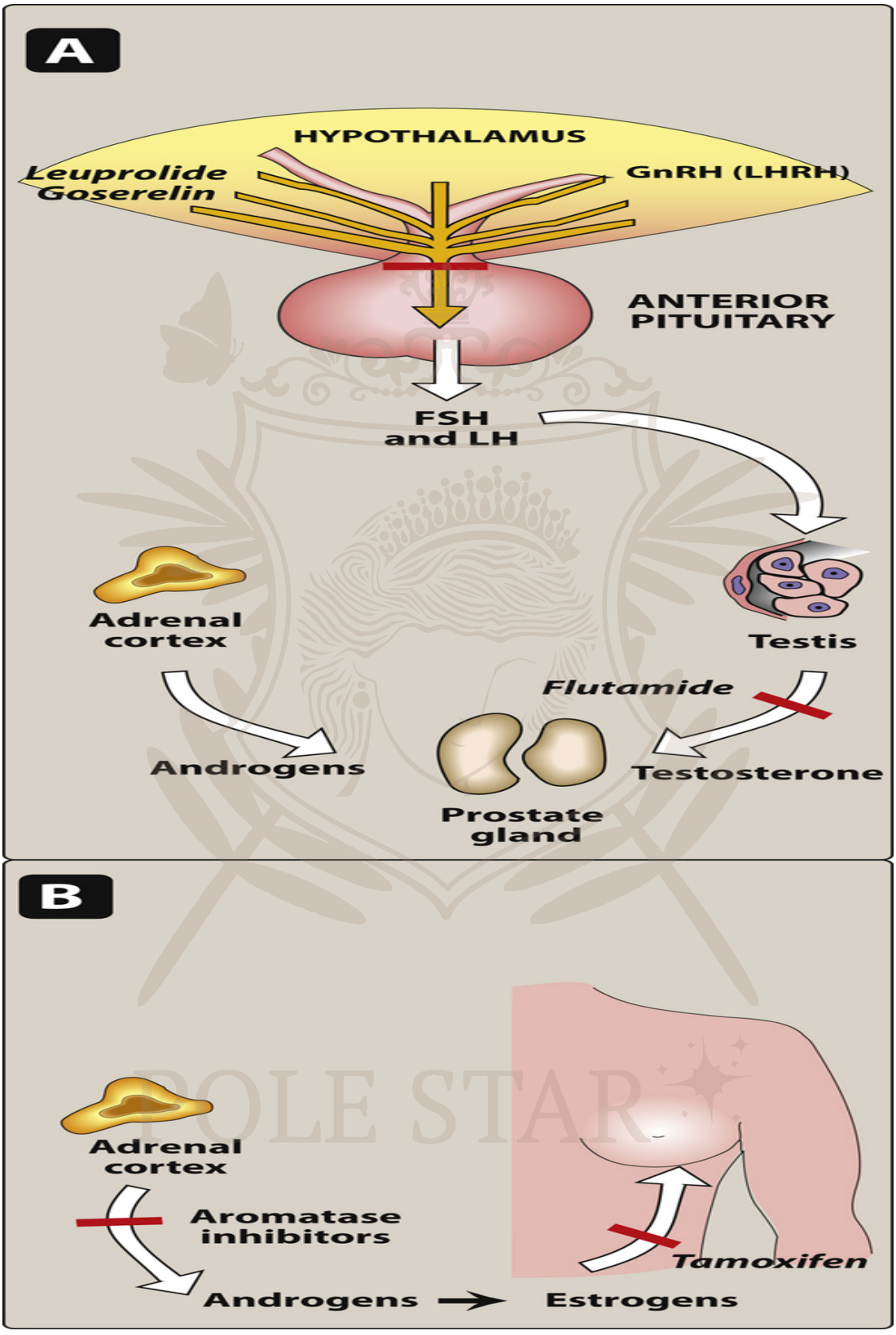
A
HYPOTHALAMUS
Leuprolide
Goserelin
GnRH (LHRH)
ANTERIOR
PITUITARY
FSH
and LH
Adrenal
cortex
Testis
Flutamide
Androgens
Testosterone
Prostate
gland
B
Adrenal
cortex
Aromatase
inhibitors
Tamoxifen
Androgens
Estrogens

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Figure 37.27 Effects of some anticancer drugs on the endocrine system.**A**, In therapy for prostatic cancer. **B**, In therapy of postmenopausal breast cancer. FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; LHRH = luteinizing hormone–releasing hormone.

E. Antiandrogens

Flutamide [FLOO-ta-mide], *apalutamide* [a-pa-LOO-ta-mide], *darolutamide* [DAR-oh-LOO-ta-mide], *nilutamide* [nye-LOO-ta-mide], *bicalutamide* [bye-ka-LOO-ta-mide], and *enzalutamide* [enz-a-LOO-ta-mide] are oral antiandrogens used in the treatment of prostate cancer. They compete with the natural hormone for binding to the androgen receptor and prevent its action in the prostate (see Figure 37.27). Adverse effects include gynecomastia, constipation, nausea, and abdominal pain. Rarely, liver failure has occurred with *flutamide. Nilutamide* can cause visual problems.

VIII. TOPOISOMERASE INHIBITORS

These agents exert their mechanism of action via inhibition of topoisomerase enzymes, a class of enzymes that reduce supercoiling of DNA (Figure 37.28).

DRUG	ROUTE	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
Irinotecan	IV	Diarrhea, myelosuppression, N, V	CYP3A4 substrates	CBC, electrolytes	Acute and delayed (life-threatening) diarrhea
Topotecan	IV, PO	Myelosuppression, N, V	P-glycoprotein inhibitors (PO)	CBC	Diarrhea common with PO
Etoposide	IV, PO	Myelosuppression, hypotension, alopecia, N, V		CBC	May cause secondary malignancies (leukemias)

Figure 37.28 Summary of topoisomerase inhibitors.CBC = complete blood count; IV = intravenous; N = nausea; PO = oral administration; V = vomiting.

A. Camptothecins

Camptothecins are plant alkaloids originally isolated from the Chinese tree Camptotheca. *Irinotecan* [eye-rin-oh-TEE-kan] and *topotecan* [toe-poe-TEE-kan] are semisynthetic derivatives of *camptothecin*

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[camp-toe-THEE-sin]. *Topotecan* is used in metastatic ovarian cancer when primary therapy has failed and also in the treatment of small cell lung cancer. *Irinotecan* is used with *5-FU* and *leucovorin* for the treatment of colorectal carcinoma.

1.Mechanism of action: The topoisomerases relieve torsional strain in DNA by causing reversible, single-strand breaks. These drugs are S phase specific and inhibit topoisomerase I, which is essential for the replication of DNA in human cells (Figure 37.29). SN-38 (the active metabolite of *irinotecan*) is approximately 1000 times as potent as *irinotecan* as an inhibitor of topoisomerase I.

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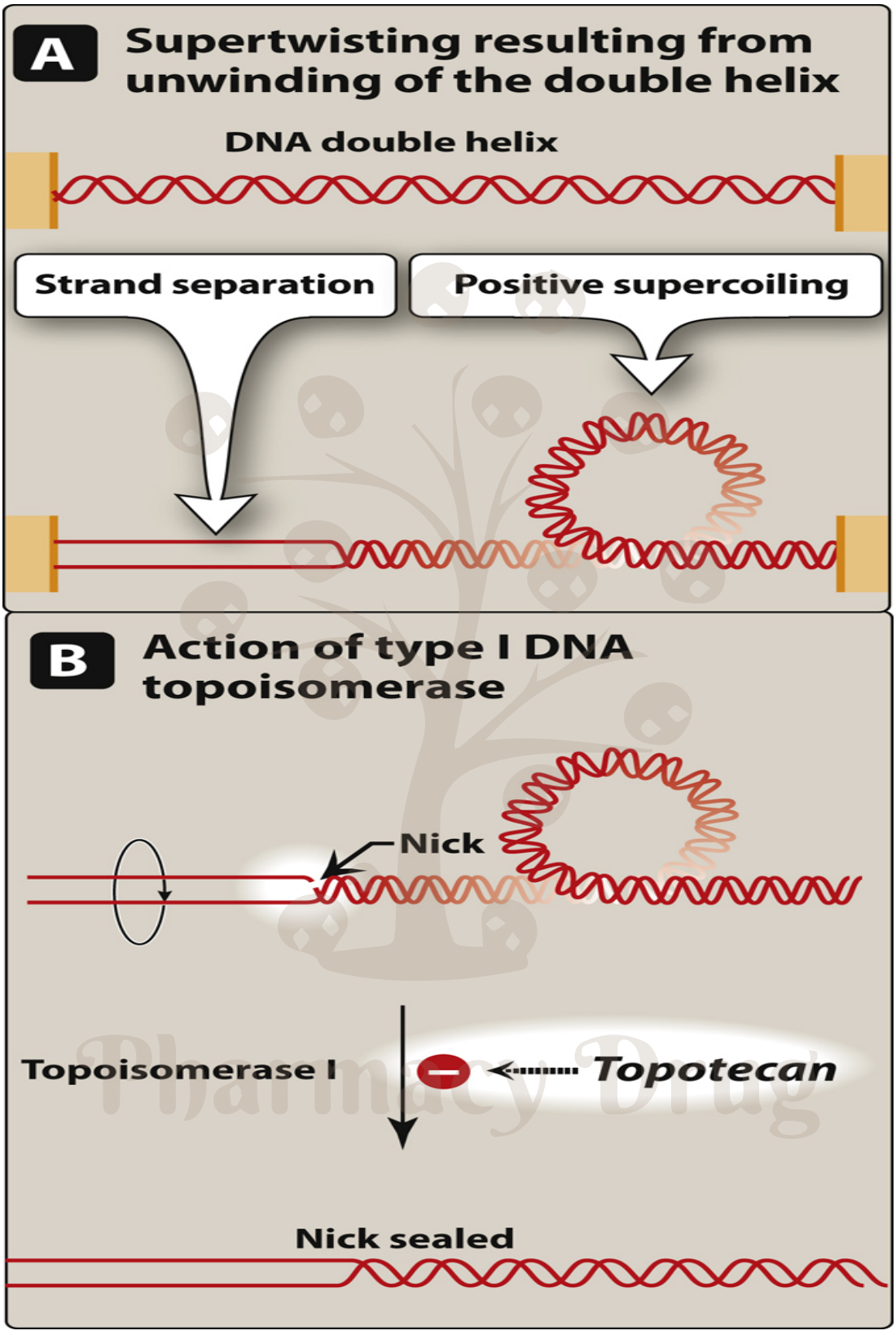

Figure 37.29 Action of type I DNA topoisomerases.

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2.Adverse effects: Bone marrow suppression, particularly neutropenia, is the dose-limiting toxicity for *topotecan.* Frequent blood counts should be performed in patients receiving this drug. Myelosuppression is also seen with *irinotecan.* Acute and delayed diarrhea with *irinotecan* may occur. The acute form occurs within 24 hours and is thought to be due to cholinergic effects; therefore, it can be treated with *atropine.* The late form, which is due to the toxic metabolite, SN-38, causing direct mucosal damage, may be severe and potentially life-threatening. It requires treatment with high doses of *loperamide* in the days following the infusion. Since SN-38 is metabolized by UDP (UGT) A1, patients with abnormalities in this enzyme are highly susceptible to *irinotecan* toxicity.

B. Etoposide

Etoposide [e-toe-POE-side] is a semisynthetic derivative of the plant alkaloid, podophyllotoxin. This agent blocks cells in the late S to G_2 phase of the cell cycle, and the major target is topoisomerase II. Binding of the drug to the enzyme–DNA complex results in persistence of the transient, cleavable form of the complex and, thus, renders it susceptible to irreversible double-strand breaks (Figure 37.30). *Etoposide* finds its major clinical use in the treatment of lung cancer and in combination with *bleomycin* and *cisplatin* for testicular carcinoma. *Etoposide* may be administered either IV or orally. Dose-limiting myelosuppression (primarily leukopenia) is the major toxicity. It can also cause infusion-related hypotension.

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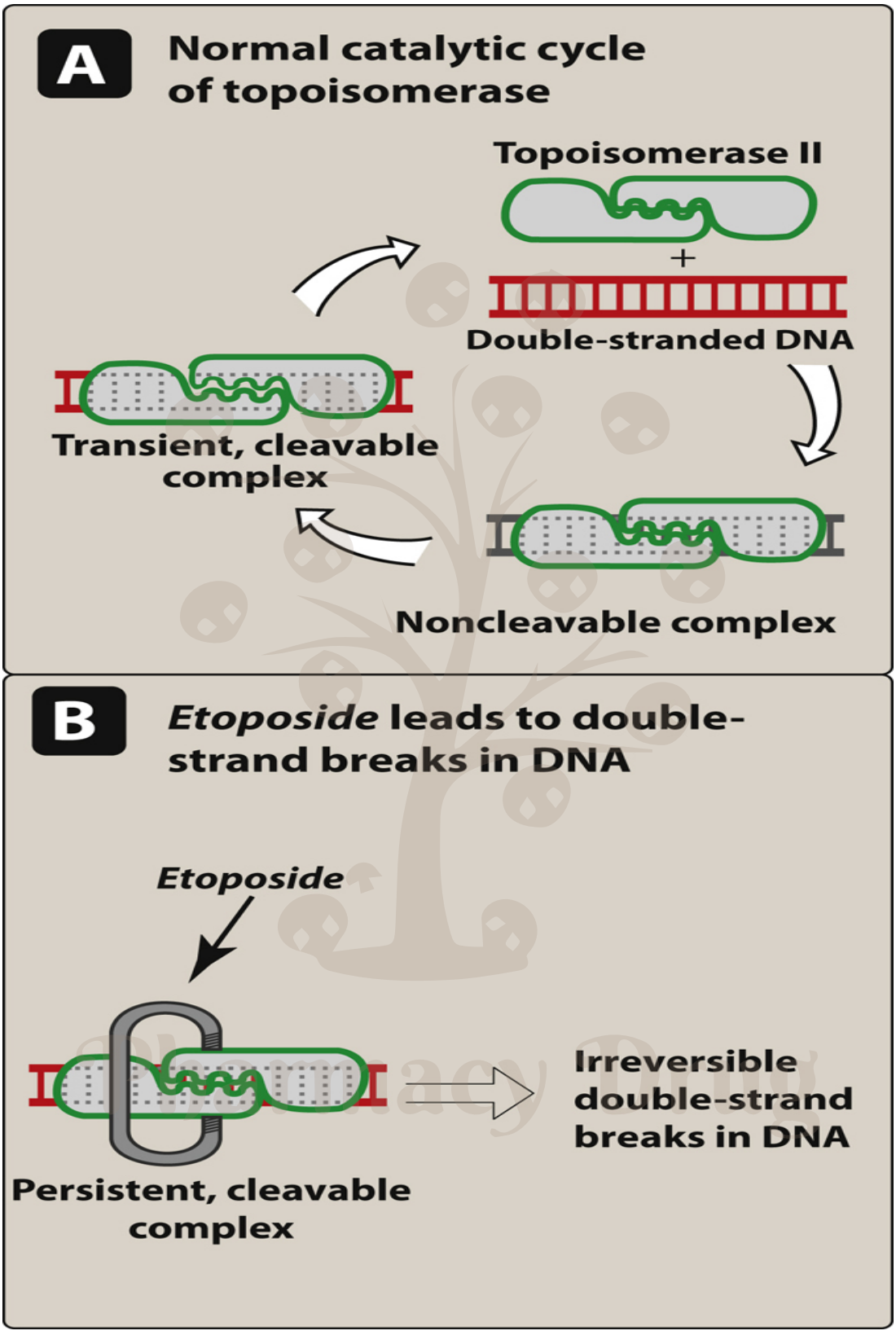

Figure 37.30 Mechanism of action of *etoposide*.

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IX. ANTIBODIES

Monoclonal antibodies (Figure 37.31) are an active area of drug development for anticancer therapy and other nonneoplastic diseases, because they are directed at specific targets and often have different adverse effect profiles as compared with traditional chemotherapy agents. [Note: Monoclonal antibodies also find application in a number of other disorders, such as inflammatory bowel disease, psoriasis, and rheumatoid arthritis.] All of these agents are administered intravenously, and infusion-related reactions are common.

MONOCLONAL ANTIBODY	ANTIBODY TARGET	NOTES
Bevacizumab	VEGF	Withold pre/post surgery, increases risk of bleeding, avoid with anthracyclines
Cetuximab	EGFR	May cause cardiopulmonary arrest or serious infusion reactions; premedication with antihistamine required before infusion
Panitumumab	EGFR	Causes high incidence of dermatologic reactions
Rituximab	CD20	Causes TLS and infusion reactions, hepatitis B reactivation, and progressive multifocal leukencephalopathy; premedication with antihistamine and *acetaminophen*
Trastuzumab	HER2	Monitor for heart failure; causes infusion reactions and pulmonary toxicity
Brentuximab	CD30	Antibody-drug conjugate with microtubule inhibitor attached, dose-limiting neurotoxicity

Figure 37.31 Summary of monoclonal antibodies.EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor protein 2; TLS = tumor lysis syndrome; VEGF = vascular endothelial growth factor.

X. KINASE INHIBITORS

The kinases are a family of enzymes that are involved in several important processes within a cell, including signal transduction and cell division. [Note: At least 50 kinases mediate cell growth or division by phosphorylation of signaling proteins. They have been implicated in the development of many neoplasms.] Kinase inhibitors most often mimic ATP to prevent ATP binding and subsequent phosphorylation of substrates. The kinase inhibitors are administered orally, and these

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agents have a wide variety of applications in the treatment of cancer (Figure 37.32).

Clinical Application 37.2: Revisiting Resistance

Acquired resistance occurs when a patient stops responding to a treatment after an initial response. **Primary resistance** occurs when a patient never responds to a treatment. Primary and acquired resistance are common with targeted therapies like kinase inhibitors. Patients with activating mutations in KRAS have primary resistance to kinase inhibitors that work upstream of RAS, like the epidermal growth factor receptor inhibitor, *erlotinib.* Many patients who take kinase inhibitors ultimately develop a mutation in the ATP-binding site of the kinase that permits ATP to bind preferentially over the kinase inhibitor. This is a form of acquired resistance.

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KINASE INHIBITOR	KINASE TARGET	NOTES
Afatinib	EGFR FAMILY	Administer on empty stomach; monitor for development of heart failure
Crizotinib	ALK, ROS	Administer with antiemetics
Dasatinib	SRC FAMILY, BCR-ABL	Monitor bone growth/density and for development of heart failure; avoid with PPIs
Erdafitinib	FGFR FAMILY	Restrict phosphate intake
Erlotinib	EGFR FAMILY	Rash correlates with response
Ibrutinib	BTK	Monitor for heart failure; may also be used for chronic refractory graft-versus-host-disease; can cause secondary malignancies
Idelalisib	PI3K	Monitor for infections
Imatinib	BCR-ABL	First tyrosine kinase inhibitor; monitor for development of heart failure
Lapatinib	EGFR FAMILY	Can cause severe hepatotoxicity and severe diarrhea; monitor for heart failure and lung pneumonitis
Midostaurin	FLT3	Administer with antiemetics
Pralsetinib	RET	Monitor for hemorrhage, hepatotoxicity, pneumonitis, TLS, and wound healing impariment
Ruxolitinib	JAK FAMILY	Increased risk of VTE; may also be used for acute graft-versus-host-disease
Sorafenib	VEGF FAMILY	Wound healing complications, cardiac events
Trametinib	MEK1/2	Used only in patients with BRAFV600E mutation
Vemurafenib	BRAF MUTATIONS	Monitor for heart failure; avoid with *doxorubicin*, *topotecan*, and *vincristine*

Figure 37.32 Summary of kinase inhibitors.ALK = anaplastic lymphoma kinase; BCR-ABL = breakpoint cluster region-abelson; BTK = Bruton tyrosine kinase; EGFR = epidermal growth factor receptor; FGFR = fibroblast growth factor receptor; FLT3 = FMS-like tyrosine kinase 3; JAK = Janus associated kinase; MEK = mitogen-activated extracellular signal-regulated kinase; P13K = phosphatidylinositol-3-kinase; PPI = proton pump inhibitor; RET = rearranged during transfection; TLS = tumor lysis syndrome; VEGF = vascular endothelial growth factor; VTE = venous thromboembolism.

XI. IMMUNOTHERAPY

POLESTAR

Immunotherapy with intravenous immune checkpoint inhibitors is a rapidly evolving option for cancer treatment. The goal of immune checkpoint inhibitors is to block the checkpoint molecules, such as the programmed death (PD-1) receptor, that normally help to keep the immune system in check. By blocking these molecules, the immune system is better able to attack the tumor and cause destruction. The most commonly used checkpoint inhibitors are *pembrolizumab* [PEM-broe-LIZ-ue-mab] and *nivolumab* [nye-VOL-ue-mab], which block the PD-

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1 receptor on T cells. *Atezolizumab* [a-te-zoe-LIZ-ue-mab] and *avelumab* [a-VEL-ue-mab] block the PD-1 ligand directly on the tumor cell, and *ipilimumab* [ip-i-LIM-u-mab] blocks the CTLA-4 receptor on T cells (Figure 37.33). The adverse-reaction profiles of these agents consist of potentially severe and even fatal immune-mediated adverse events. This is because turning off the immune checkpoints allows attack of the tumor, but it can also lead to unchecked autoimmune response to normal tissues. Adverse events include diarrhea, colitis, pneumonitis, hepatitis, nephritis, neurotoxicity, dermatologic toxicity in the form of severe skin rashes, and endocrinopathies such as hypo- or hyperthyroidism. Patients should be closely monitored for the potential development of signs and symptoms of toxicity and promptly treated with corticosteroids if necessary.

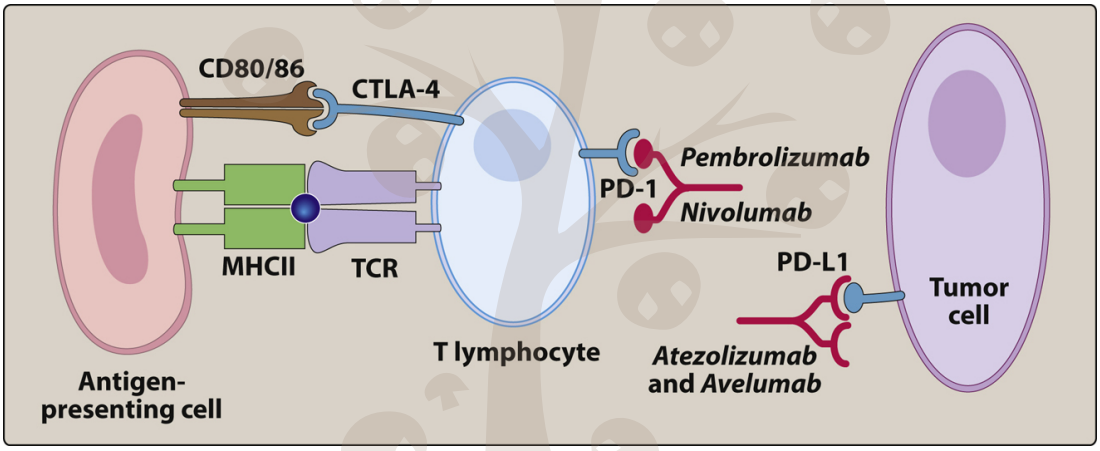

Figure 37.33 Mechanism of action of immune checkpoint inhibitors.CTLA-4 = cytotoxic T-lymphocyte antigen 4; MHC = major histocompatibility complex; PD = programmed death; TCR = T-cell receptor.

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XII. CELLULAR AND GENE THERAPY PRODUCTS

A. Gene therapies

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Tisagenlecleucel [tis-a-jen-lek-LOO-sel] is a genetically modified autologous T cell administered intravenously. To create *tisagenlecleucel*, a patient's own T cells are harvested and genetically modified to express a chimeric antigen receptor (CAR) that activates the T cell based on a specific cell surface marker on the tumor. Patients are given lymphodepleting chemotherapy (usually *fludarabine* and *cyclophosphamide*) prior to autologous T-cell transfusion (Figure 37.34). *Tisagenlecleucel* is used to treat refractory acute lymphoblastic leukemias and diffuse large B-cell lymphomas. The principal toxicities, which can be fatal, are a cytokine release storm and/or neurologic toxicities, including encephalopathy, cerebral edema, seizures, or leukoencephalopathy. *Axicabtagene ciloleucel* [ax-i-CAB-tay-jeen sye-LO-loo-sel], *lisocabtagene maraleucel* [LIH-soh-KAB-tuh-jeen MAR-uh-LOO-sel], and *brexucabtagene autoleucel* [BREX-ue-KAB-ta-jeen AW-toe-LOO-sel] are additional genetically modified T-cell therapies used to treat refractory hematologic malignancies.

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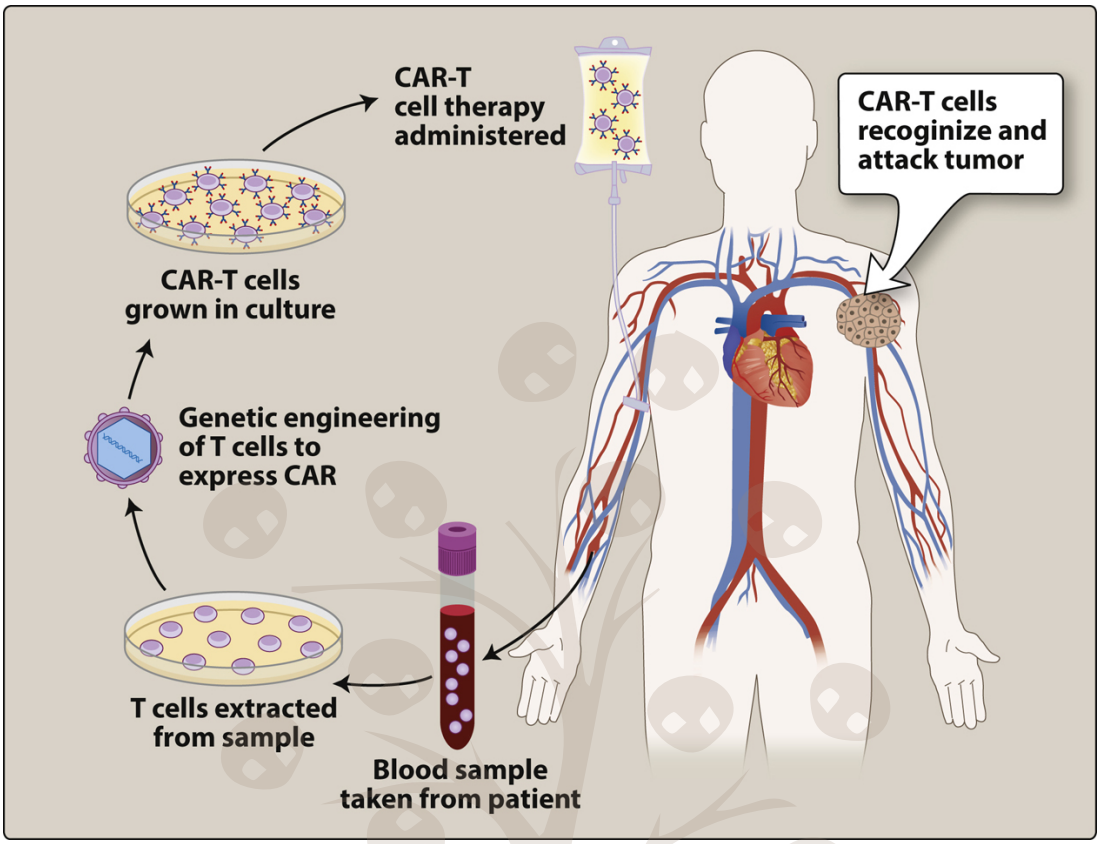

Figure 37.34 Gene and cell therapies for cancer.

B. Cellular products

Sipuleucel-T [si-pu-LOO-sel-tee] is an autologous immunotherapy given by IV infusion consisting of antigen presenting cells (APCs), T cells, B cells, natural killer (NK) cells, and other cells. These cells are collected from the patient by leukaphoresis, then activated by incubation with a recombinant protein, PAP-GM-CSF. PAP-GM-CSF is a prostate cancer antigen coupled to a hematopoietic growth factor that stimulates immune cell activation. *Sipuleucel-T* is used in the treatment of metastatic castration–resistant prostate cancer. The main adverse effects are infusion reactions, thrombolytic events, and vascular disorders such as stroke and myocardial infarction.

XIII. MISCELLANEOUS AGENTS

A. Abiraterone acetate

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Abiraterone [ab-er-AT-er-own] *acetate* is an oral agent used in the treatment of metastatic castration–resistant prostate cancer. *Abiraterone acetate* is used in conjunction with *prednisone* to inhibit the CYP17 enzyme (an enzyme required for androgen synthesis), resulting in reduced testosterone production. Coadministration with *prednisone* is required to help lessen the effects of mineralocorticoid excess resulting from CYP17 inhibition. Hepatotoxicity may occur, and patients should be closely monitored for hypertension, hypokalemia, and fluid retention. Joint and muscle discomfort, hot flushes, and diarrhea are common adverse effects with this agent.

B. Immunomodulating agents

Thalidomide [tha-LID-oh-mide], *lenalidomide* [LEN-a-LID-oh-mide], and *pomalidomide* [pom-a-LID-oh-mide] are oral agents used in the treatment of multiple myeloma. Their exact mechanism of action is not clear, but they possess antimyeloma properties including antiangiogenic, immune-modulation, anti-inflammatory, and antiproliferative effects. These agents are often combined with *dexamethasone* or other chemotherapeutic agents. Adverse effects include thromboembolism, myelosuppression, fatigue, rash, and constipation. *Thalidomide* was previously given to pregnant women to prevent morning sickness. However, severe birth defects were prevalent in children born to mothers who used *thalidomide.* Because of their structural similarities to *thalidomide*, *lenalidomide* and *pomalidomide* are contraindicated in pregnancy.

C. Proteasome inhibitors

Bortezomib [bore-TEZ-o-mib], *ixazomib* [ix-az-O-mib], and *carfilzomib* [kar-FIL-zo-mib] are proteasome inhibitors commonly used as the backbone therapy in the treatment of multiple myeloma. These agents work by inhibiting proteasomes, which in turn prevents the degradation of proapoptotic factors, thus leading to a promotion in programmed cell death (apoptosis). Malignant cells readily depend on suppression of the apoptotic pathway; therefore, proteasome inhibition works well in multiple myeloma. *Bortezomib* can be administered IV, but the subcutaneous route is preferred because it is associated with less neuropathy. Other adverse effects include myelosuppression, diarrhea, nausea, fatigue, and herpes zoster reactivation. Patients

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should receive antiviral prophylaxis if they are receiving therapy with *bortezomib. Ixazomib* is an oral agent with an adverse-effect profile similar to that of *bortezomib. Carfilzomib* is administered intravenously, and common adverse effects include myelosuppression, fatigue, nausea, diarrhea, and fever.

"Chemo Man" is a useful tool to help remember the most common toxicities of these drugs (Figure 37.35).

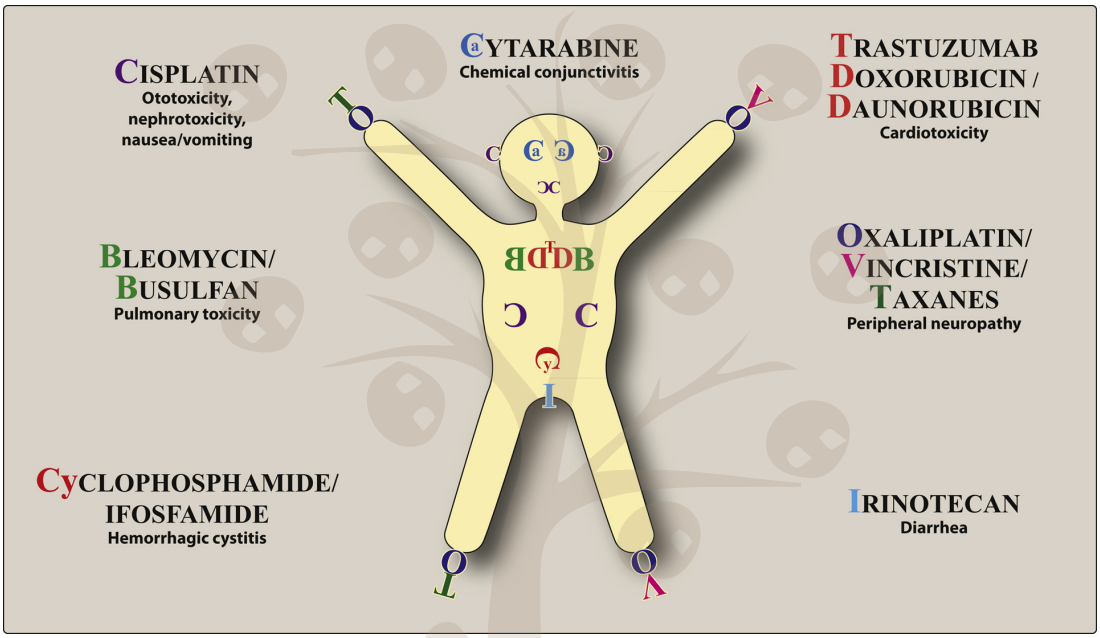

Figure 37.35 Chemo Man—a summary of toxicity of chemotherapeutic agents.

Chapter Summary

- Anticancer drugs work to reduce the cancer burden to cure patients or to provide relief from symptoms and improve quality of life.
- Anticancer drugs may be given alone or in combination as adjuvant chemotherapy following surgery or radiation, as neoadjuvant chemotherapy prior to surgery or radiation, or as maintenance therapy to prolong remission from cancer.
- The main classes of anticancer drugs are the antimetabolites, antitumor antibiotics, alkylating agents, microtubule inhibitors, steroid hormones and antagonists, monoclonal antibodies, kinase inhibitors, immune checkpoint inhibitors, and others, including topoisomerase inhibitors.

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- The microtubule inhibitors, antimetabolites, topoisomerase inhibitors, and *bleomycin* all inhibit the cell at specific phases of the cell cycle making them more useful for malignancies where a large percentage of the cancer cells are actively dividing at any given moment. The other classes of drugs are cell cycle nonspecific and have more utility when the growth fraction of the cancer cells is low or unknown.
- The most common dose-limiting toxicities of chemotherapy (and the drugs that cause them) include hemorrhagic cystitis (*cyclophosphamide*/*ifosfamide*), pulmonary toxicity (*bleomycin*/*busulfan*), ototoxicity with nephrotoxicity and nausea/vomiting (*cisplatin*), cardiotoxicity (*doxorubicin*/*daunorubicin*/*trastuzumab*), peripheral neuropathies (*oxaliplatin*/*vincristine*/taxanes), and potentially fatal diarrhea (*irinotecan*).
- Drugs like corticosteroids, antivirals, antibiotics, antihistamines, chemoprotectants, and hematopoietic growth factors may be given as concomitant therapies to reduce the risk of adverse effects of anticancer agents.

STUDY QUESTIONS

Choose the ONE best answer.

37.1 A patient is about to undergo one cycle of chemotherapy following surgery for breast cancer. Which of the following best describes chemotherapy in this setting?

A. Adjuvant
B. Neoadjuvant
C. Palliative
D. Maintenance

Correct answer = A. Chemotherapy is used as a supplemental treatment to attack micrometastases *following* surgery and radiation treatment, in which case it is called adjuvant chemotherapy. Chemotherapy is also given before surgical procedures in an attempt to shrink the cancer, and this is referred to as neoadjuvant chemotherapy. Chemotherapy is indicated when neoplasms are disseminated and are not amenable to surgery (palliative). Chemotherapy given in lower doses to assist in prolonging remission is known as maintenance chemotherapy.

37.2 Which of the following drugs is most likely to inhibit a cancer cell in S phase?

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A. Pemetrexed
B. Docetaxel
C. Dacarbazine
D. Epirubicin

Correct answer = A. Pemetrexed is an antimetabolite with a mechanism similar to methotrexate. The antimetabolites have maximal cytotoxic effects in S phase. Docetaxel is a microtubule stabilizer that prevents breakdown of microtubules that is required for cell division. It arrests cells in M phase. Epirubicin and dacarbazine are both cell cycle nonspecific.

37.3 A 45-year-old woman is being treated with docetaxel, doxorubicin, and cyclophosphamide chemotherapy for breast cancer. She just completed six cycles and now has developed shortness of breath, fatigue, and swelling in her feet. Further workup reveals a reduced left ventricular ejection fraction. Which of the following drugs is the most likely cause of her symptoms?

A. Doxorubicin
B. Docetaxel
C. Cyclophosphamide
D. Dexamethasone

Correct answer = A. Doxorubicin can cause irreversible, dose-dependent cardiotoxicity. This risk increases with cumulative dose and is greater in people over 60 years and people with other cardiovascular risk factors like smoking, hypertension, diabetes, dyslipidemia, and obesity.

37.4 A 64-year-old man is scheduled to undergo chemotherapy for chronic lymphocytic leukemia, and the regimen includes cyclophosphamide. Which of the following is most appropriate to include in chemotherapy orders for this patient?

A. IV hydration, mesna, and frequent urinalyses
B. Leucovorin and frequent urinalyses
C. Allopurinol and frequent urinalyses
D. IV hydration, prophylactic antibiotics, and frequent urinalyses

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Correct answer = A. A unique toxicity of cyclophosphamide is hemorrhagic cystitis. This bladder toxicity has been attributed to toxic metabolites of cyclophosphamide. Adequate hydration as well as IV injection of mesna (sodium 2-mercaptoethane sulfonate), which neutralizes the toxic metabolites, can minimize this problem. Frequent urinalyses to monitor for red blood cells should be ordered. Leucovorin is used with methotrexate or 5-FU (not cyclophosphamide). Allopurinol has a drug interaction with cyclophosphamide and is not an agent that prevents hemorrhagic cystitis. IV fluids are correct; however, mesna is also needed.

37.5 A patient with rhabdomyosarcoma is being treated with vincristine and dactinomycin. By what mechanism is the vincristine working to reduce the tumor burden in this patient?

A. Alkylation of DNA
B. Disruption of microtubule assembly
C. Inhibition of DNA synthesis
D. Modulation of estrogen response

Correct answer = B. Vincristine is a vinca alkaloid and inhibitor of microtubules. It is used for many types of soft tumors and hematologic malignancies. Neurologic effects of the drug may be dose limiting.

37.6 Which of the following chemotherapy drugs can cause cold-induced peripheral neuropathy and liver enzyme abnormalities?

A. Cyclophosphamide
B. Oxaliplatin
C. Etoposide
D. Cisplatin

Correct answer = B. Oxaliplatin can cause bone marrow suppression, GI toxicity, hepatotoxicity, hypersensitivity reactions, and neuropathies that are exacerbated by the cold. Cisplatin can cause renal failure, neuropathy, hearing loss, electrolyte wasting, and significant nausea and vomiting. Cyclophosphamide and etoposide have myelosuppression as the dose-limiting toxicity.

37.7 Which of the following is the most efficient inhibitor of peripheral estrogen synthesis that is commonly used to treat breast cancer in postmenopausal women?

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A. Tamoxifen
B. Raloxifene
C. Anastrozole
D. Fulvestrant

Correct answer = C. Anastrozole is an aromatase inhibitor that is very effective in reducing nonadrenal estrogens, which makes it ideal for use in postmenopausal females. Tamoxifen and raloxifene are selective estrogen receptor modulators, and fulvestrant is an estrogen receptor downregulator. None of the other choices decrease estrogen synthesis.

37.8 A patient is treated with a multidrug regimen for advanced testicular cancer, and he subsequently develops an acute leukemia 6 years later. Which of the following drugs, included in the patient's initial treatment regimen, likely contributed to the tumorigenesis of the leukemia?

A. Paclitaxel
B. Gemcitabine
C. Vinblastine
D. Etoposide

Correct answer = D. Etoposide may cause secondary malignancies when used alone or in conjunction with other therapies. It may be used with cisplatin and ifosfamide to treat testicular cancer, both of which increase its propensity to cause secondary malignancies. Paclitaxel, gemcitabine, and vinblastine may be used to treat testicular cancer, but none of these agents cause secondary malignancies.

37.9 A patient with Burkitt lymphoma develops hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia following combination chemotherapy treatment. Which of the following drugs was most likely used as part of the combination therapy?

A. Rituximab
B. Azacitidine
C. Imatinib
D. Bevacizumab

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Correct answer = A. Rituximab is a CD-20 antibody that is used in B-cell malignancies. It can cause tumor lysis syndrome in patients with high numbers of circulating malignant cells or high tumor burden. Imatinib and azacitidine may cause tumor lysis syndrome but are not used in Burkitt lymphoma, and bevacizumab is not used in diffuse large B-cell lymphoma and does not cause tumor lysis syndrome.

37. 10 Nivolumab and ipilimumab are used to treat a patient with non–small cell lung cancer. Which of the following adverse effects is most likely to occur following treatment with these drugs?

A. Cardiotoxicity
B. Colitis
C. Hemorrhagic cystitis
D. Secondary malignancy

Correct answer = B. Immune checkpoint inhibitors cause diarrhea, colitis, pneumonitis, hepatitis, nephritis, and neurotoxicity, among other things. They are not known for causing cardiotoxicity, hemorrhagic cystitis, or secondary malignancies.

POLE STAR

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38

Immunosuppressants

Maya Leiva, Jody K. Takemoto

I. OVERVIEW

The immune system is one of the most complex systems in the body. While the function of the immune system is to protect the body against harmful nonself molecules, alterations of immunological mediators can elicit a cascade of undesirable effects. Autoimmune diseases (for example, inflammatory bowel disease, multiple sclerosis, lupus, psoriasis, and rheumatoid arthritis) can arise when the immune system mistakenly identifies an individual's own tissues as foreign and directs a destructive response against them. The goal of treatment in autoimmune diseases is to use drug therapy to stop this inappropriate and harmful process. In the case of organ transplantation, foreign tissue is purposely implanted into the recipient, but the goal remains the same—to use drug therapy to limit the damage inflicted by the immune system and potential rejection of the transplanted organ. Immunosuppressants are drugs that reduce the activation or efficacy of the immune system to treat autoimmune diseases or to lower the body's ability to reject a transplanted organ. Transplantation of organs and tissues has become routine due to improved surgical techniques, advances in tissue typing, and the availability of more effective immunosuppressive therapies. The principal approach to immunosuppressive therapy is to alter lymphocyte function using drugs or antibodies against immune proteins. Immunosuppressant agents important for transplant are listed in Figure 38.1. [Note: Although this chapter focuses on immunosuppressive agents in the

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context of organ transplantation, these agents may be used in the treatment of other disorders. For example, *cyclosporine* may be useful in the treatment of psoriasis, and various monoclonal antibodies have applications in a number of disorders, including rheumatoid arthritis, multiple sclerosis, Crohn disease, and ulcerative colitis.]

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ANTIBODIES

Alemtuzumab CAMPATH
Antithymocyte globulins ATGAM, THYMOGLOBULIN
Basiliximab SIMULECT
Rituximab RITUXAN

CALCINEURIN INHIBITORS

Cyclosporine NEORAL, SANDIMMUNE
Tacrolimus ASTAGRAF XL, ENVARSUS XR, PROGRAF

COSTIMULATION BLOCKER

Belatacept NULOJIX

mTOR INHIBITORS

Everolimus ZORTRESS
Sirolimus RAPAMUNE

ANTI-PROLIFERATIVES

Azathioprine IMURAN
Mycophenolate mofetil CELLCEPT
Mycophenolate sodium MYFORTIC

ADRENOCORTICOIDS

Methylprednisolone MEDROL SOLU-MEDROL
Prednisolone ORAPRED, PRELONE
Prednison GENERIC ONLY

OTHER

Belimumab BENLYSTA
Bortezomib VELCADE
Eculizumab SOLIRIS
Intravenous immunoglobulin VARIOUS
Tofacitinib XELJANZ

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Figure 38.1 Immunosuppressant drugs.mTOR = mammalian target of *rapamycin*.

A. Rationale for use of immunosuppressants

During organ transplantation, the recipient's body is introduced to nonself tissue through implantation. [Note: An allograft is a transplant of an organ or tissue from one person to another who is not genetically identical.] Immunosuppressants are used to help prevent undesirable immune responses that cause the body to attack itself and to prevent rejection of the transplanted organ. When used in the induction and maintenance of organ transplant, immunosuppressants can selectively inhibit rejection of transplanted tissues, prevent the patient from immunological compromise, and prolong the life of transplanted organs. The ideal outcome of treatment is to maintain the patient's host defenses while increasing donor-specific tolerance. In addition, it is important to minimize adverse effects and the risk of infection. The management of the immune activation cascade is fundamental to obtaining these goals.

B. Immune activation cascade

The immune activation cascade can be described as a three-signal model (Figure 38.2). Signal 1 constitutes T-cell triggering at the CD3 receptor complex by an antigen on the surface of an antigen-presenting cell (APC). Signal 1 alone is insufficient for T-cell activation and requires signal 2. Signal 2, also referred to as costimulation, occurs when CD80 and CD86 on the surface of APCs engage CD28 on T cells. Both signals 1 and 2 activate several intracellular signal transduction pathways, one of which is the calcium–calcineurin pathway. These pathways trigger the production of cytokines such as interleukin (IL)-2. IL-2 then binds to the IL-2 receptor (also known as CD25) on the surface of other T cells, thereby providing signal 3, activating the cell cycle via

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mammalian target of *rapamycin* (mTOR), and leading to T-cell proliferation.

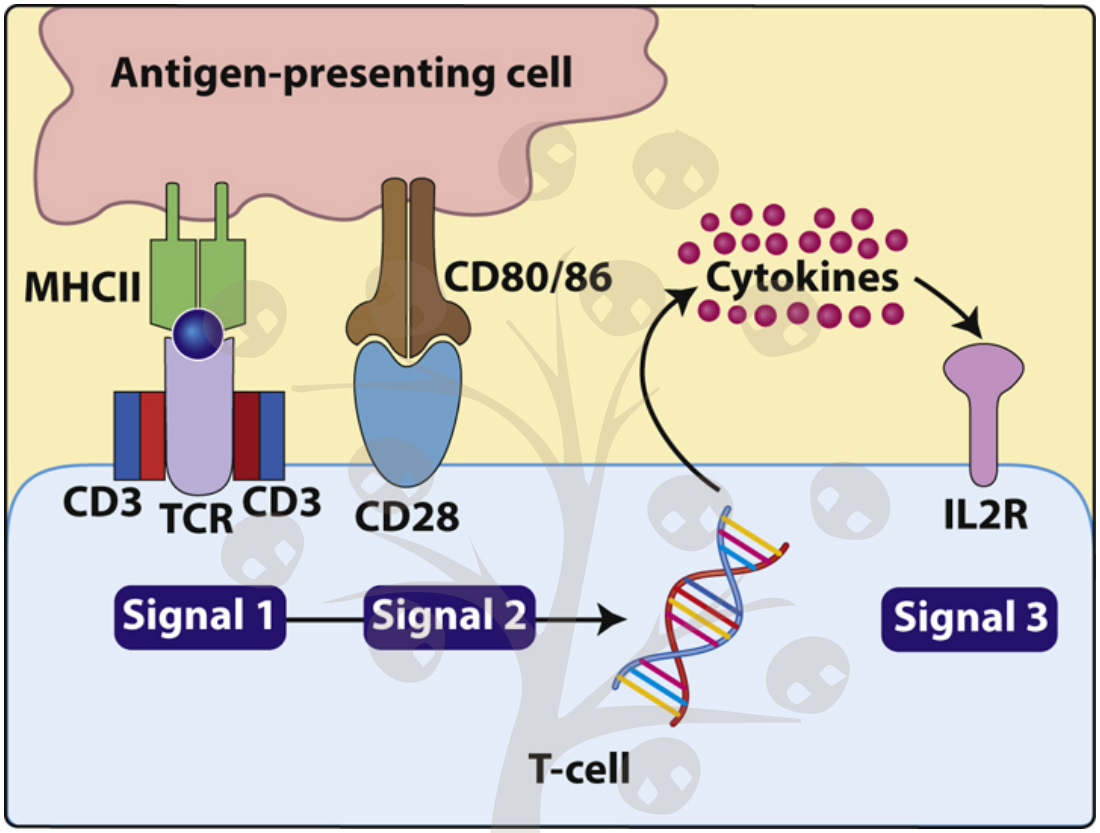

Figure 38.2 Simplified immune activation cascade.IL2 = interleukin 2; MHC = major histocompatibility complex; TCR = T-cell receptor.

C. Basic principles of immunosuppressant therapy in transplantation

Immunosuppressants are broadly categorized by phase in transplant therapy (induction, maintenance, or treatment of rejection) and mechanism of action (Figure 38.3). Immunosuppressive drug regimens typically consist of two to four agents with different mechanisms of action that disrupt various levels of T-cell activation. Monoclonal and polyclonal antibodies are often used in induction therapy, which powerfully suppresses

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the immune system at the time of transplant to allow the new organ to start functioning in the recipient and prevent early graft rejection. Immunosuppressant drugs used for maintenance therapy are typically less toxic and are often prescribed in lower doses to provide long-term immunological protection for the transplanted organs. Maintenance drugs often carry a lower risk of infection compared with drugs used for induction, although the risk for opportunistic infections is still increased throughout the duration of therapy. During maintenance therapy, a combination of agents is frequently used at lower doses to maintain adequate immunosuppression while minimizing adverse effects. Antirejection therapies are selected based on the target organ or tissue and type of rejection.

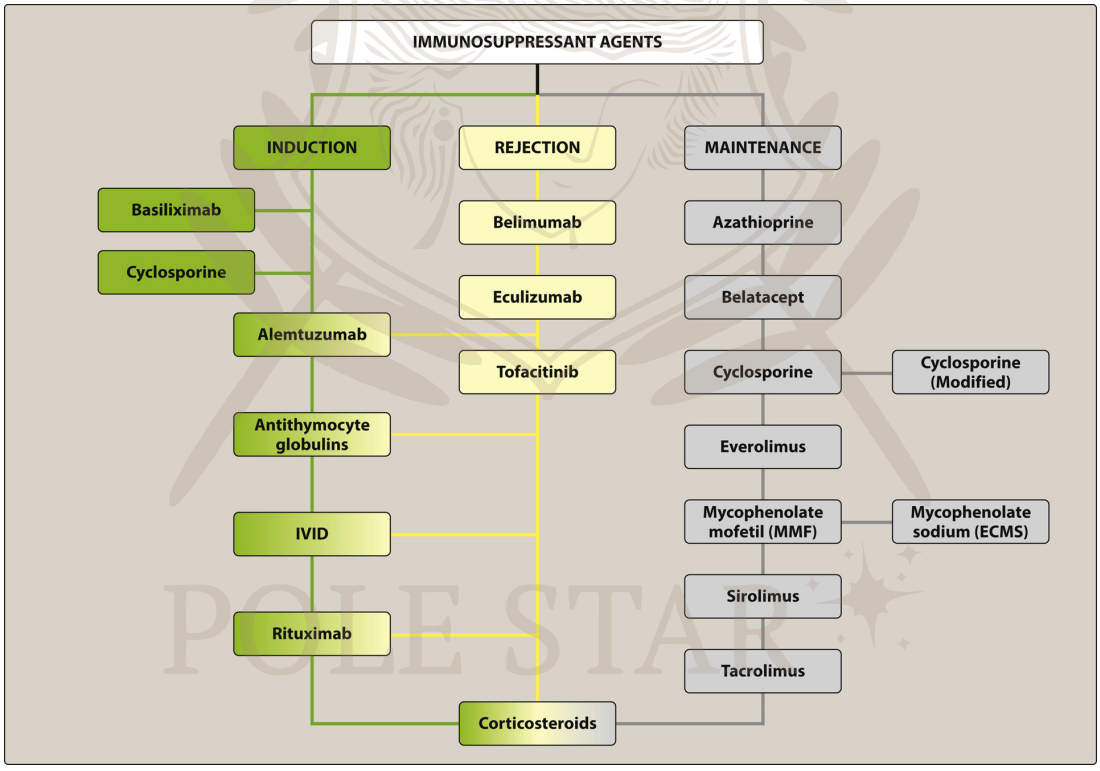

Figure 38.3 Immunosuppressant agents categorized by role in therapy.IVIG = intravenous immunoglobulin.

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II. IMMUNOSUPPRESSANT DRUGS FOR INDUCTION AND REJECTION

Immunosuppressants play an integral role during the induction and rejection phase of immunosuppression for solid organ transplant. The goal of induction therapy is to provide short-term, broad immunosuppression in the early posttransplant period, when the risk of acute allograft rejection is highest. Induction therapy often involves the use of antibodies and/or higher doses of the medications used in maintenance therapy for approximately 2 weeks (Figure 38.4).

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DRUG	CLASS	MECHANISM OF ACTION	INDICATIONS	ADVERSE EFFECTS
Alemtuzumab	Humanized monoclonal antibody	Binds to CD52 on B and T lymphocytes, causing T- and B-cell depletion	Induction, treatment of rejection	Infusion-related effects (chills, fever), severe and prolonged leukopenia, neutropenia, thrombocytopenia, infections (CMV, HSV, and other viruses/fungi)
Antithymocyte globulins	Polyclonal antibody	T-cell depletion	Induction, treatment of rejection	Infusion-related effects (chills, fever), leukopenia, thrombocytopenia, pulmonary edema, infections due to CMV or other viruses, skin rash
Basiliximab	Chimeric monoclonal antibody	IL-2 receptor antagonist on activated T-lymphocytes (nondepleting)	Induction	Generally well tolerated vs. placebo
Bortezomib	Proteasome inhibitor	Proteasome inhibition leads to plasma cell depletion	Treatment of antibody-mediated rejection	Leukopenia, anemia, thrombocytopenia, nausea/vomiting, diarrhea, peripheral neuropathy, hypotension, hepatotoxicity (less common)
Intravenous Immunoglobulin (IVIG)	Immune globulin	Exact mechanism of action unknown and likely multifactorial	Induction for highly sensitized patients, treatment of rejection	Infusion-related reactions, headache, hypotension, hemolytic anemia, pulmonary edema, thromboembolic events, aseptic meningitis, acute renal failure
Methylprednisolone	Corticosteroid	Nonspecific interleukin and TNF inhibition	Induction, treatment of rejection, maintenance	HTN, HLD, hyperglycemia, peripheral edema, mood disturbance, osteoporosis, weight gain
Rituximab	Chimeric monoclonal antibody	Binds to the CD20 antigen on B lymphocytes, mediating B cell lysis (depletion)	Induction, treatment of rejection	Infusion-related effects (chills, fever), infections (reactivation of hepatitis B virus, CMV, and other viruses/fungi), PML, leukopenia, thrombocytopenia, mucocutaneous reactions

Figure 38.4 Medications used for induction and/or rejection immunosuppressant therapy.CMV = cytomegalovirus; HLD = hyperlipidemia; HSV = herpes simplex virus; HTN = hypertension; IL = interleukin; PML = progressive multifocal leukoencephalopathy; TNF = tumor necrosis factor.

Treatment for rejection can be initiated in combination with induction therapy, if induction therapy fails or when a patient starts to show signs of rejection. The goal for treatment of rejection is to attenuate the host's immune response and prevent irreversible injury to the grafted organ. The pathophysiology associated with the type of rejection (cellular or humoral immunity) influences choice of treatment. Acute rejection most commonly occurs 1 week to 3 months post-transplantation but may occur at any time. If treated early, it may be possible to minimize irreversible damage of organ tissue. Chronic rejection typically occurs months to years post-transplantation. While immunosuppressants can be used to mitigate or eliminate acute transplant rejection, they are sometimes ineffective in managing chronic transplant rejection. In these

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instances, other therapeutic options (for example, plasmapheresis) may be required, including addressing the underlying pathological etiologies.

Antibodies play a central role in prolonging allograft survival. They are prepared by immunization of either rabbits or horses, typically, with human lymphoid cells (producing a mixture of polyclonal antibodies or monoclonal antibodies) or by hybridoma technology (producing antigen-specific monoclonal antibodies). Hybridomas are produced by fusing mouse antibody-producing cells with tumor cells. Hybrid cells are selected and cloned, and the antibody specificity of the clones is determined. Clones of interest can be cultured in large quantities to produce clinically useful amounts of the desired antibody. Recombinant deoxyribonucleic acid (DNA) technology can also be used to replace part of the mouse gene sequence with human genetic material, thus "humanizing" the antibodies and making them less antigenic. The names of the monoclonal antibodies contain the suffix "-mab," which identifies the category of drug, in this case, monoclonal antibody. In addition, the names of monoclonal antibodies conventionally contain the infix "xi" if they are chimerized (for example, *basili<u>xi</u>mab*, *ritu<u>xi</u>mab*) and "zu" if they are humanized (for example, *alemtu<u>zu</u>mab*). In contrast to monoclonal antibodies, which are homogeneous and specific, polyclonal antibodies are variable and less specific.

A. Alemtuzumab

Alemtuzumab [AL-em-TOOZ-ue-mab] is a humanized monoclonal antibody that binds to CD52 on both T and B cells, resulting in depletion of both lymphoid cell lines. Depletion of T and B cells is observed soon after infusion and recovery of these cells is gradual. T cells recover over 6–12 months, and B cells recover in 6 months or less. It is approved for the treatment of chronic lymphocytic leukemia and multiple sclerosis but has been used in transplantation as an induction and antirejection agent for both acute cellular rejection and antibody-mediated rejection (AMR) due to its activity against both T and B cells. Because of the

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potent and prolonged immunosuppressive effect, it is recommended to initiate or continue prophylaxis for Pneumocystis pneumonia and herpes viruses after administration of *alemtuzumab*.

B. Antithymocyte globulins

Antithymocyte globulins [AN-tahy-THAHY-muh-sahyt-GLOB-yuh-lins] are polyclonal antibodies produced by isolating gamma-globulin fractions of serum obtained from rabbits or horses after immunization with human thymocytes. They cause depletion of circulating T cells and apoptosis of activated T cells. Rabbit preparations are preferred over horse preparations because of greater potency and less toxicity. The rabbit-derived *antithymocyte globulin* is primarily used at the time of transplantation to prevent early allograft rejection, along with other immunosuppressive agents. It may also be used to treat severe rejection episodes or corticosteroid-resistant acute rejection. It is usually used for 3–10 days to produce profound lymphopenia that may last beyond 1 year. The antibodies are slowly infused by intravenous (IV) infusion. Premedication with corticosteroids, *acetaminophen*, and antihistamines may help reduce infusion-related reactions. Prolonged use may be associated with profound immunosuppression leading to an increased risk of opportunistic infections and posttransplant lymphoproliferative disease (PTLD).

C. Basiliximab

Basiliximab [bass-il-IX-im-ab] is a chimeric murine/human monoclonal antibody that binds to the α chain of the IL-2 receptor (CD25) on activated T cells and, thus, interferes with the proliferation of these cells. Blockade of this receptor foils the ability of any antigenic stimulus to activate the T-cell response system. *Basiliximab* is approved for prophylaxis of acute rejection in renal transplantation in combination with *cyclosporine* and corticosteroids. This may allow for reduced doses or delayed introduction of calcineurin inhibitors. *Basiliximab* may be beneficial in those with delayed graft function and may reduce the risk of

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calcineurin inhibitor–associated renal toxicity. Since it is not T-cell-depleting, *basiliximab* is mainly used in induction protocols for the prophylaxis of acute rejection, as opposed to the treatment of rejection. It is administered as an IV infusion and, unlike many other agents, does not require premedications. *Basiliximab* is generally well tolerated, although it may cause adverse effects such as hypertension and gastrointestinal (GI) distress. The incidence of opportunistic infections and lymphoproliferative disorders may be increased.

D. Rituximab

Rituximab [ri-TUX-i-mab] is a chimeric monoclonal antibody against the antigen CD20 on pre-B-cells, mature B cells, and memory B cells. *Rituximab* causes B-cell depletion by inducing B-cell lysis and blocking B-cell activation and eventual maturation to antibody-forming plasma cells. Existing plasma cells do not express the CD20 antigen and therefore are unaffected by *rituximab.* The drug is approved for use in the treatment of B-cell lymphomas, PTLD, and rheumatoid arthritis. The benefit of using *rituximab* in transplantation is for antibody removal, which has been utilized in ABO (blood type)-incompatible transplants, desensitization protocols, and treatment of AMR.

Intravenous administration of *rituximab* leads to rapid and sustained depletion of B lymphocytes, with B-cell counts returning to normal within 9–12 months. *Rituximab* has a boxed warning for reactivation of JC virus leading to progressive multifocal leukoencephalopathy (PML), which has been reported in the nontransplant population. Activation of hepatitis B infection has also been reported following treatment, and hepatitis serologies should be monitored.

Clinical Application 38.1: Considerations for Rituximab Therapy

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Since *rituximab* is a chimeric monoclonal antibody, there is an increased chance of infusion-related reactions, particularly during the first infusion. Premedication with *acetaminophen*, corticosteroids, and *diphenhydramine* can minimize the severity of such reactions. Like many monoclonal antibodies, mild to moderate *rituximab* infusion reactions are associated with chills, fever, mild hypotension, dyspnea, and rash. Severe reactions are less common and are, among other symptoms, associated with severe hypotension, anaphylaxis, and cardiac dysfunction. *Rituximab* also increases the risk of infection. For example, hepatitis B (HBV) reactivation is believed to occur because *rituximab* induces CD4 lymphopenia and this results in a reduced number of CD4 memory T cells, subsequently impairing immunity against viruses like HBV. Cytomegalovirus, progressive multifocal leukoencephalopathy, parvovirus, and herpes zoster are other infectious diseases associated with immunosuppressive effects of *rituximab*.

E. Bortezomib

AMR involves the production of high levels of antibodies by plasma cells, either newly made from B cells or from those that existed prior to transplant. One mechanism to control AMR is to target antibody production by plasma cells. *Bortezomib* [bor-TEZ-oh-mib] is a proteasome inhibitor that leads to cell-cycle arrest and apoptosis of normal plasma cells, thereby decreasing antibody production in sensitized patients. *Bortezomib* is approved for the treatment of multiple myeloma and certain types of lymphoma, but it has also been used in the treatment of AMR in transplant patients. This agent can be administered via IV bolus or subcutaneous injection and has a low potential for infusion-related reactions.

F. Intravenous immunoglobulin

Intravenous immunoglobulin (*IVIG*) contains immunoglobulins prepared by human plasma pooled from many donors. It has an immunomodulatory effect and is often used for autoimmune diseases, pretransplant desensitization protocols, and treatment of AMR. [Note: *IVIG* has many approved indications, including chronic inflammatory demyelinating polyneuropathy, immune thrombocytopenic purpura, and immunodeficiency syndromes.]

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The immunomodulatory effects on T and B cells occur at high doses, and it is also used at lower doses to prevent infection by replacing immunoglobulins removed during plasmapheresis. The mechanism of action is not well defined, but high doses of *IVIG* appear to induce B-cell apoptosis and modulate B-cell signaling. It also inhibits binding of antibodies to the transplanted graft and activation of the complement system. The serum half-life of *IVIG* is about 3–4 weeks. Adverse effects of *IVIG* include headache, fever, chills, myalgias, and hypotension/hypertension, which can be reduced by slowing the infusion rate and/or administering premedications. Serious adverse effects are rare and can include aseptic meningitis, acute renal failure, and thrombotic events.

III. MAINTENANCE IMMUNOSUPPRESSANT MEDICATIONS

Maintenance immunosuppressants are intended to provide adequate immunosuppression to prevent allograft rejection while minimizing infection, malignancy, and drug-induced adverse effects. Maintenance therapy is initiated at the time of surgery and is continued indefinitely to prevent loss of the allograft. Often, maintenance immunosuppressants are combined in regimens of two to four drugs, using medications with different mechanisms of action to minimize drug toxicity. These drugs can be further divided into four main classes: (1) calcineurin inhibitors (*cyclosporine* and *tacrolimus*), (2) costimulation blocker (*belatacept*), (3) mTOR inhibitors (*sirolimus* and *everolimus*), and (4) antiproliferatives (*azathioprine and mycophenolate*) (Figure 38.5).

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DRUG	CLASS	INDICATIONS	PHARMACOKINETICS	ADVERSE EFFECTS
Azathioprine	Antiproliferative	SOT (renal), RA, lupus	Activated by glutathione S-transferase DDIs (*allopurinol*, ACE inhibitors, *warfarin*)	Myelosuppression, nausea, vomiting, diarrhea, pancreatitis, hepatotoxicity
Belatacept	Costimulation blocker	SOT (renal)	Elimination half-life ~10 days	Anemia, leukopenia, diarrhea, increased risk of PTLD
Cyclosporine	Calcineurin inhibitor	SOT (renal, liver, heart), psoriasis, RA, GVHD	Metabolism by CYP3A4 Numerous DDIs Inhibitor of CYP3A4 and P-glycoprotein	HTN, HLD, hyperglycemia, hyperkalemia, hirsutism, gingival hyperplasia, neurotoxicity, nephrotoxicity
Everolimus	mTOR inhibitor	SOT (renal, liver), oncology	Metabolism by CYP3A4 Numerous DDIs	HTN, HLD (particularly TG, TC), stomatitis, proteinuria, impaired wound healing, rash, myelosuppression
Methylprednisolone, prednisolone, prednisone	Corticosteroid	Numerous indications	Activated to *prednisolone*	HTN, HLD, hyperglycemia, peripheral edema, mood disturbance, osteoporosis, weight gain
Mycophenolate	Antiproliferative	SOT (renal, liver, heart)	Metabolism by glucuronidation DDI (bile acid sequestrants; antacids for MMF)	Leukopenia, thrombocytopenia, nausea, vomiting, diarrhea
Sirolimus	mTOR inhibitor	SOT (renal, heart), lymphangio-leiomyomatosis, GVHD	Metabolism by CYP3A4 Numerous DDIs	HTN, HLD (particularly TG, TC), stomatitis, proteinuria, impaired wound healing, rash, myelosuppression, pneumonitis
Tacrolimus	Calcineurin inhibitor	SOT (renal, liver, heart), GVHD	Metabolism by CYP3A4 Numerous DDIs	HTN, HLD, hyperglycemia, hyperkalemia, alopecia, neurotoxicity (hand tremor, headache, seizure), nephrotoxicity

Figure 38.5 Medications used for maintenance immunosuppressant therapy.ACE = angiotensin-converting enzyme; DDI = drug–drug interaction; GVHD = graft-versus-host disease; HLD = hyperlipidemia; HTN = hypertension; MMF = *mycophenolate mofetil*; mTOR = mammalian target of *rapamycin*; PTLD = posttransplant lymphoproliferative disorder; RA = rheumatoid arthritis; SOT = solid organ transplant; TC = total cholesterol; TG = triglycerides.

A. Calcineurin inhibitors

Calcineurin inhibitors *cyclosporine* [sye-kloe-SPOR-een] and *tacrolimus* [tac-RO-li-mus] block signal transduction through the calcium–calcineurin pathway, activated downstream of signal 1, to impair T-cell activation. Calcineurin, a calcium-dependent protein phosphatase, dephosphorylates nuclear factor of activated T cells (NFAT), allowing NFAT to enter the T-cell nucleus and bind to DNA, leading to transcription and production of cytokines, including IL-2. *Cyclosporine* binds to the immunosuppressant binding protein cyclophilin, whereas *tacrolimus* binds to a protein

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called FK-binding protein (FKBP). These drug–protein complexes inhibit the enzymatic activity of calcineurin, thereby preventing T-cell activation. *Cyclosporine* is used in prevention of transplant rejection in kidney, liver, and heart transplant. It may also be used in the management of graft-versus-host disease (GVHD). *Tacrolimus* is the preferred calcineurin inhibitor due to its decreased rate of allograft rejection as compared with *cyclosporine.* This agent is a mainstay of maintenance immunosuppressant therapy in many solid organ transplants and may also be used in the management of GVHD. Patients who cannot tolerate *cyclosporine* and those who experience rejection while on treatment with *cyclosporine* may benefit from a switch in therapy to *tacrolimus*.

One of the primary limitations to the use of calcineurin inhibitors is nephrotoxicity, which has led to the development of regimens using lower doses of these agents in combination with other immunosuppressant drugs. Enzymes CYP3A4/5 and P-glycoprotein (P-gp) expressed in the GI tract and liver are responsible for the interindividual variability in oral absorption and metabolism of *cyclosporine* and *tacrolimus*, and both agents are subject to numerous drug interactions. Therapeutic drug monitoring is recommended for the calcineurin inhibitors. As with all immunosuppressants, infections are possible with use of calcineurin inhibitors, and recipients are often given anti-infective prophylactic medications post transplant. Other potential side effects include hypertension, headache, and tremor. Hirsutism, or excessive hair growth, and gingival hyperplasia are potential adverse effects of *cyclosporine*.

B. Costimulation blocker

Costimulation is a secondary signal used by immune cells to fully activate an immune response in conjunction with the primary signal (Figure 38.2). Costimulation blockers typically interfere with the secondary signal (signal 2) to diminish the immune response, and, thus, reduce the potential for rejection. *Belatacept* [bel-a-TA-

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sept], a costimulation blocker, is a recombinant fusion protein of CTLA-4, which like CD28, binds to CD80 and CD86 on APCs. Binding of *belatacept* to CD80 and CD86 prevents CD28 from binding to those molecules and, thus, inhibits signal 2 of the T-cell activation pathway. *Belatacept* is approved for kidney transplantation in combination with *basiliximab*, *mycophenolate mofetil* (*MMF*), and corticosteroids. This drug can substitute for calcineurin inhibitors to avoid the detrimental long-term nephrotoxic, cardiovascular, and metabolic complications seen with *cyclosporine* and *tacrolimus*. *Belatacept* is administered by IV infusion. Clearance of the drug is not affected by age, sex, race, renal, or hepatic function. *Belatacept* increases the risk of PTLD, particularly of the central nervous system. For this reason, it is contraindicated in patients who are seronegative to Epstein–Barr virus (EBV), a common cause of PTLD. Serological titers to EBV are typically obtained to confirm exposure.

C. mTOR inhibitors

Sirolimus [sih-RO-lih-mus] (also known as *rapamycin*) and *everolimus* [e-ve-RO-lih-mus] inhibit the protein mTOR, blocking the signal transduction pathway activated by signal 3. Progression into the cell cycle and T-cell proliferation is subsequently prevented (Figure 38.6). The mTOR inhibitors are commonly used in multidrug regimens, frequently to minimize the dose of calcineurin inhibitors and spare their nephrotoxic adverse effects. Both agents are used for rejection prophylaxis for organ transplantation. *Sirolimus* may also be used in the prevention and treatment of GVHD, and *everolimus* is also used in oncology to treat different types of cancer. The antiproliferative action of *sirolimus* is also valuable in cardiology where *sirolimus*-coated stents are used to inhibit restenosis of the blood vessels by reducing proliferation of the endothelial cells.

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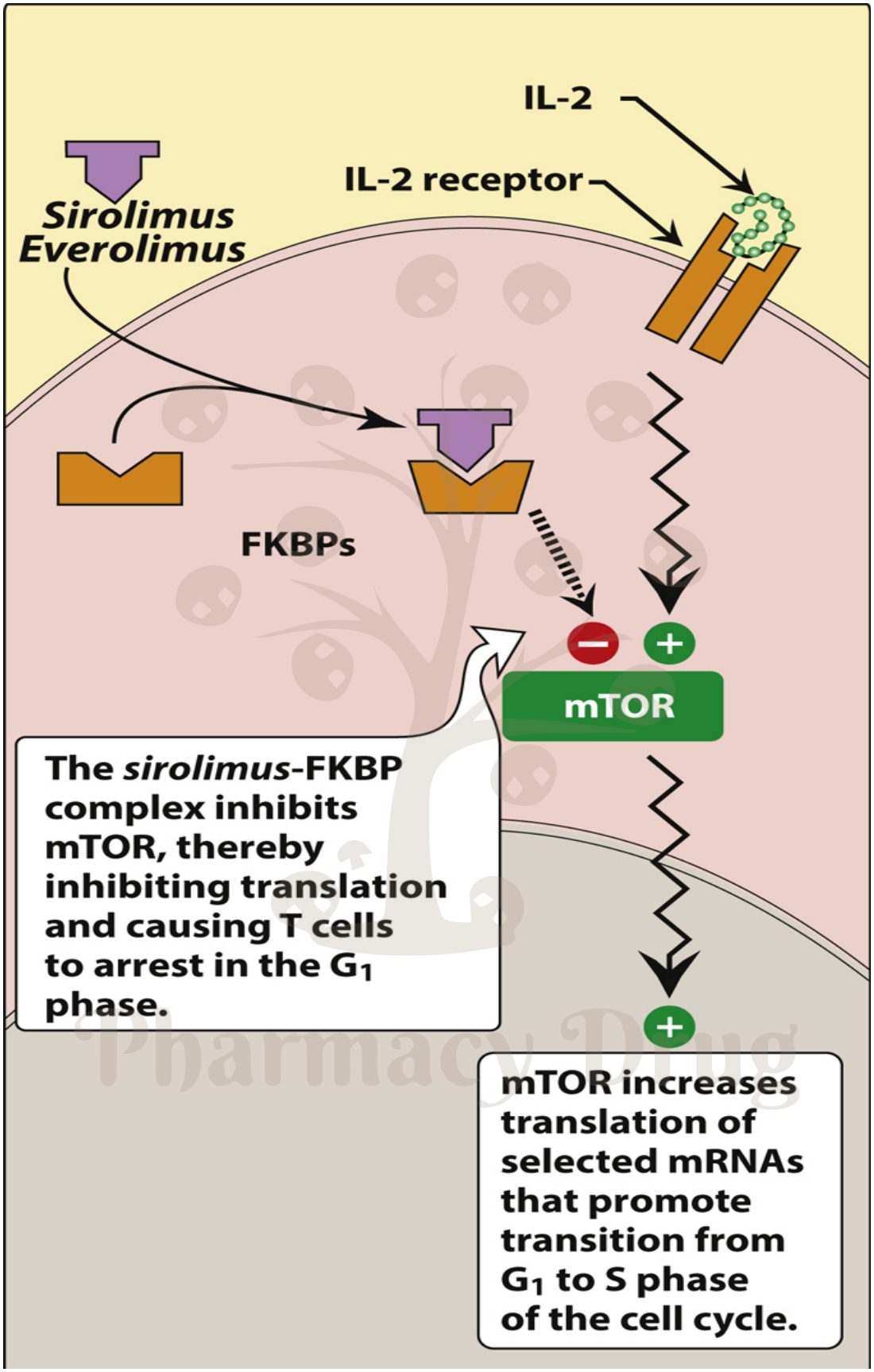

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Figure 38.6 Mechanism of action of *sirolimus* and *everolimus*.FKBP = FK-binding protein; IL = interleukin; mRNA = messenger RNA; mTOR = mammalian target of *rapamycin*.

Like the calcineurin inhibitors, both *sirolimus* and *everolimus* are substrates of CYP3A4 and P-gp, and, therefore, are subject to numerous drug–drug interactions. Both agents require drug monitoring to optimize therapy. *Sirolimus* has a longer half-life than calcineurin inhibitors or *everolimus.* Adverse effects of these agents may include metabolic effects (hypercholesterolemia, hypertriglyceridemia), hematologic effects (leukopenia, thrombocytopenia, anemia), and GI distress (nausea, vomiting, constipation, diarrhea). Long-term exposure may also increase the risk of new-onset diabetes.

Clinical Application 38.2: Therapeutic Drug Monitoring for Calcineurin Inhibitors and mTOR Inhibitors

The calcineurin inhibitors *cyclosporine* and *tacrolimus*, and the mTOR inhibitors *everolimus* and *sirolimus,* have a narrow therapeutic index (see Chapter 1). This means that small alterations in blood concentration of the drug can cause potentially serious effects, including therapeutic failure if levels are too low, or life-threatening adverse drug reactions if levels are too high. For this reason, therapeutic drug monitoring (TDM) must be used to ensure that the patient has an acceptable systemic concentration of medication. The rationale behind TDM is to simultaneously maximize immunosuppression to prevent allograft rejection and minimize significant and potentially irreversible toxicity associated with drugs with a narrow therapeutic index. Specific TDM protocols and standard ranges for drug concentration for each agent may vary slightly by target organ and/or institution.

D. Antiproliferatives

Complex signaling cascades are required for the proliferation of various cell types. Antiproliferative agents (antimetabolites) act by inhibiting various targets in the signaling cascade, thus reducing

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immune cell proliferation and moderating cytotoxic immune response. The antiproliferatives *azathioprine* [ay-za-THYE-oh-preen] and *mycophenolate* [mye-koe-FEN-oh-late] block lymphocyte proliferation by inhibiting nucleic acid synthesis. These medications are used as adjunctive immunosuppressant agents, primarily with calcineurin inhibitors with or without corticosteroids. However, *mycophenolate* has largely replaced *azathioprine* in this role due to its improved safety and efficacy profile.

Azathioprine, which was one of the first agents to achieve widespread use in organ transplantation, is a prodrug that is converted first to *6-mercaptopurine* (*6-MP*) and then to the corresponding nucleotide analogue, thioinosinic acid. The analog is incorporated into nucleic acid chains and blocks further elongation of the DNA. The main dose-limiting adverse effect of *azathioprine* is bone marrow suppression. Xanthine oxidase inhibitors (*allopurinol, febuxostat*; see Chapter 40) inhibit the metabolism of *azathioprine* and can increase the risk for toxicity. Concomitant use with *febuxostat* is contraindicated, and use with *allopurinol* should be avoided or the dose of *azathioprine* should be reduced.

Mycophenolate [mye-koe-FEN-oh-late] is a potent, reversible, noncompetitive inhibitor of inosine monophosphate dehydrogenase, which blocks the de novo formation of guanosine monophosphate (Figure 38.7). Because lymphocytes are unable to utilize the salvage pathway of nucleotide synthesis, *mycophenolate* effectively blocks T- and B-cell proliferation by eliminating de novo production of guanosine monophosphate. *Mycophenolate* is available in two formulations—as a prodrug *MMF* and as an active drug *mycophenolic acid* (*MPA*). *MMF* is rapidly hydrolyzed in the GI tract to *MPA.* Glucuronidation of *MPA* in the liver produces an inactive metabolite, but enterohepatic recirculation occurs, prolonging the effect of the drug. Adverse effects include GI distress (nausea, vomiting, diarrhea, abdominal

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pain), bone marrow suppression (anemia, leukopenia, thrombocytopenia), and increased risk of infection.

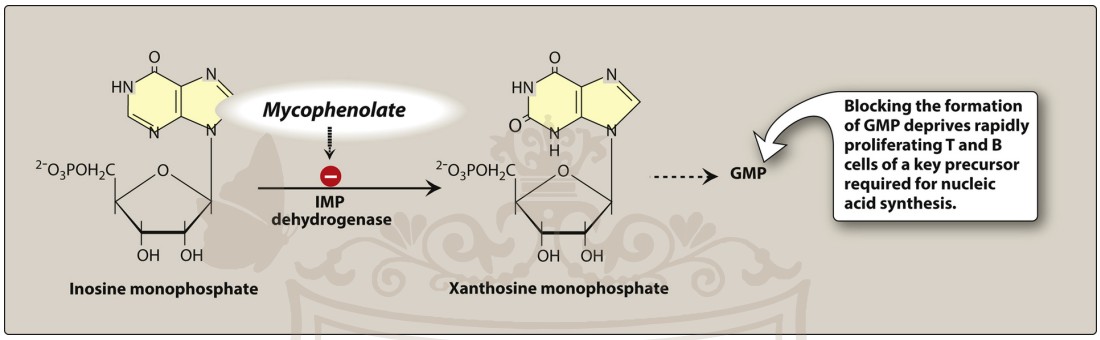

Figure 38.7 Mechanism of action of *mycophenolate*.IMP = inosine-5′-monophosphate; GMP = guanosine monophosphate.

Clinical Application 38.3: Importance of Checking the Drug Formulation for Cyclosporine and Mycophenolate

Cyclosporine is available in two chemically distinct forms, an oil-based, nonmodified formulation of *cyclosporine* and the microemulsion modified formulation of *cyclosporine.* Since the absorption of the nonmodified formulation is low and inconsistent, a modified formulation was developed. The modified formulation is substantially more bioavailable and can lead to increased levels of *cyclosporine.* Variability in absorption between the formulations exists; therefore, the formulations are not interchangeable and the products cannot be substituted for one another.

MMF is the prodrug of *MPA. MMF* can cause substantial GI distress due to its release of *MPA* in the stomach. To reduce adverse events and improve adherence, enteric-coated (EC) *MPA* (also referred to as *mycophenolate sodium*) was developed. *EC-MPA* releases *MPA* in the small intestine, thereby reducing the GI symptoms. Interestingly, *EC-MPA* may be more effective than *MMF* in diabetic patients with delayed gastric emptying, although *MMF* has a greater oral bioavailability. Similar to modified and nonmodified *cyclosporine*, *MMF* and *EC-MPA* are not directly interchangeable. [Note: 1000 mg *MMF* = 720 mg *EC-MPA*.]

As recommended by the Institute for Safe Medication Practices, prescriptions for *cyclosporine* and *mycophenolate* should clearly designate the desired

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formulation to reduce the risk of medication errors and incorrect substitutions.

E. Corticosteroids

The corticosteroids (see Chapter 26) were the first pharmacologic agents to be used as immunosuppressive therapy, both in transplantation and in various autoimmune disorders. They are still one of the mainstays for attenuating rejection episodes. For transplantation, the most common agents are *prednisone* and *methylprednisolone,* whereas *prednisone* and *prednisolone* are more commonly used for autoimmune conditions.

Corticosteroids are primarily used in combination with other immunosuppressant agents to suppress acute rejection of solid organ allografts and in chronic GVHD. Additionally, corticosteroids are effective for the management of a wide variety of autoimmune conditions, including refractory rheumatoid arthritis, systemic lupus erythematosus, temporal arteritis, and asthma. The exact mechanism responsible for the immunosuppressive action of the corticosteroids is unclear. The T lymphocytes are the most affected. The steroids are able to rapidly reduce lymphocyte populations by lysis or redistribution. On entering cells, they bind to the glucocorticoid receptor. The complex passes into the nucleus and regulates the transcription of DNA. Among the genes affected are those involved in inflammatory responses.

The use of these agents is associated with numerous adverse effects. Corticosteroids may cause GI distress; therefore, it is recommended to take them with food or after a meal. Other adverse effects include fluid retention, increased blood pressure, hyperglycemia, and changes in mood or behavior (mood swings, insomnia, confusion). Long-term use can lead to impaired wound healing, osteoporosis, myopathy, and cataracts. Consequently, efforts are being directed toward reducing or eliminating the use of steroids in the maintenance of allografts.

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The mechanism of action of immunosuppressants used in induction, maintenance, and treatment of rejection is summarized in Figure 38.8.

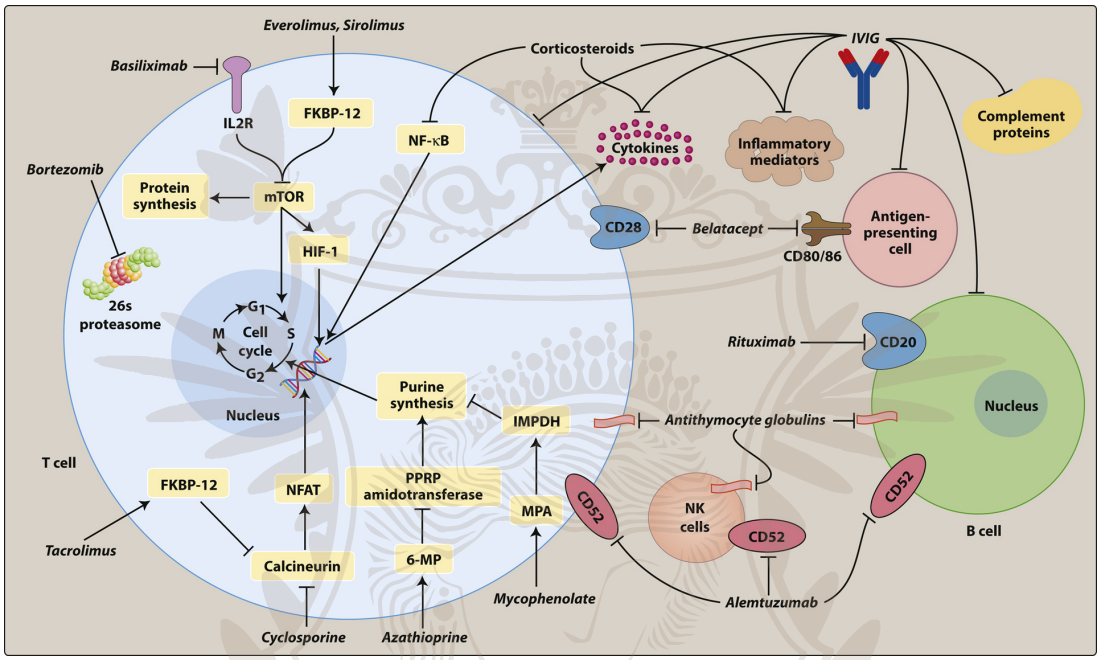

Figure 38.8 Mechanism of action of immunosuppressive agents.IL-2 = interleukin 2; IVIG = intravenous immunoglobulin; mTOR = mammalian target of *rapamycin*; NFAT = nuclear factor of activated T cells; NK = natural killer cells.

IV. OTHER IMMUNOSUPPRESSANT MEDICATIONS

Immunosuppressants that fall in this category have primary indications for other conditions; however, these agents may still be used to modulate immunosuppression.

A. Belimumab

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Belimumab [be-LIM-yoo-mab] is a fully human monoclonal antibody specific for soluble human B lymphocyte stimulator protein (BLyS). [Note: The naming convention for fully human monoclonal antibodies contains the infix "u" before the "mab" suffix.] *Belimumab* blocks the binding of soluble BLyS to its B-cell receptor, thus inhibiting B-cell survival. This inhibition also affects autoreactive B cells and further reduces B-cell differentiation into immunoglobulin-producing plasma cells. It is approved for systemic lupus erythematosus. *Belimumab* has also shown efficacy in renal and heart transplant recipients with AMR and as a possible addition to maintenance therapy. *Belimumab* carries several warnings regarding serious and fatal infections in patients receiving concurrent immunosuppressive agents and those with PML, depression and suicidality, as well as possible hypersensitivity reactions. Live vaccines are relatively contraindicated for the duration of therapy. *Belimumab* can be administered either subcutaneously or intravenously.

B. Eculizumab

Eculizumab [e-kue-LIZ-oo-mab] is a recombinant humanized monoclonal antibody that binds to the complement protein C5 with high affinity and inhibits its cleavage to C5a and C5b, ultimately preventing the formation of the terminal complement complex C5b-9. *Eculizumab* is indicated for the treatment of atypical hemolytic uremic syndrome (aHUS) through the prevention of complement-mediated thrombosis, inflammation, and lysis. *Eculizumab* may have benefit in the prevention of AMR in kidney transplant and is recommended as an alternative in the treatment of AMR.

Eculizumab is administered as an IV infusion. Although this drug is generally well tolerated, headache, nasopharyngitis, back pain, and nausea are the most commonly reported adverse effects. This agent carries a boxed warning regarding the increased risk of potentially fatal meningococcal infections. Patients must receive

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the meningococcal vaccine at least 2 weeks prior to the first dose of *eculizumab* or be given prophylactic antibiotics.

C. Tofacitinib

Tofacitinib [toe-fa-sye-ti-nib] is a targeted therapy specific for the Janus kinase (JAK) inhibitor. JAKs are a type of tyrosine kinase receptor that facilitates communication from the cell membrane to the nucleus (Figure 38.9). Ligands (cytokines) activate JAKs, leading to receptor dimerization and trans-phosphorylation on tyrosine residues. Subsequently, signal transducers and activators of transcription (STATs) in the cytoplasm are recruited to JAKs and are phosphorylated after docking. The JAK/STAT signaling pathway has significant roles in immune cell function and cell proliferation and survival. *Tofacitinib* is approved for treatment of rheumatoid arthritis (see Chapter 40), psoriatic arthritis, and ulcerative colitis, and its role in solid organ transplant is currently being explored.

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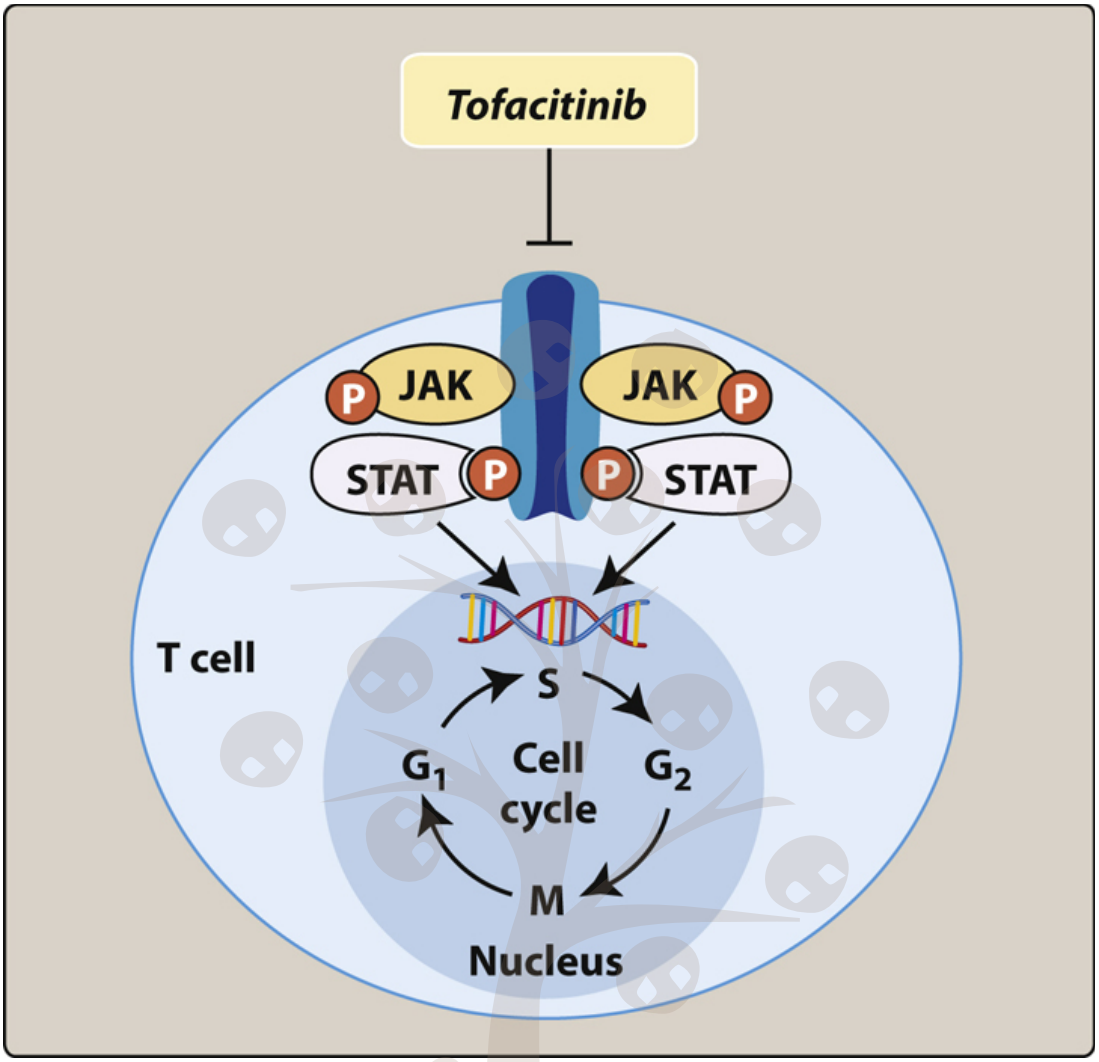

Figure 38.9 Mechanism of action of *tofacitinib*.G_1 = growth 1 phase; G_2 = growth 2 phase; JAK = Janus kinase; M = mitosis; P = phosphate; S = synthesis; STAT = signal transducer and activator of transcription.

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Common adverse effects of *tofacitinib* include increased risk of upper respiratory tract infection, nasopharyngitis, diarrhea, and headache. Drug–drug interactions can occur with drugs that modulate CYP2C19 and/or CYP3A4, and dose adjustments are recommended. Careful consideration of use and dose adjustments are recommended in patients with renal and/or hepatic impairment, lymphopenia, neutropenia, or anemia.

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Chapter Summary

- The immune system is capable of many functions, including protecting the body from nonself molecules and external invaders. Unfortunately, this system may also compromise grafted tissues when a person requires solid organ transplantation.
- Immunosuppressants are drugs used to attenuate the immune response aimed at transplanted solid organs. The focus of immunosuppression in organ transplant is on maximizing long-term outcomes of the organ and patient, and minimizing adverse effects.
- Immunosuppressants belong to diverse pharmacological classes, including but not limited to antiproliferatives, calcineurin inhibitors, corticosteroids, costimulation blockers, monoclonal antibodies, polyclonal antibodies, and mTOR inhibitors.
- Immunosuppressive agents are utilized at various points in solid organ transplant for induction, maintenance, and rejection. Some drugs, like corticosteroids, may be used for a number of indications.
- Induction therapies, including antibodies and/or intravenous immunoglobulins, are administered in the early posttransplant period to minimize acute rejection.
- Maintenance therapy used to prevent acute and chronic rejection includes calcineurin inhibitors, costimulation blockers, mTOR inhibitors, and/or antiproliferatives.
- Antirejection therapies, including antibodies, intravenous immunoglobulins, and corticosteroids are mainstays to prevent irreversible organ damage.
- When selecting immunosuppressant therapy, appropriate timing, pharmacokinetic and pharmacodynamic parameters of the drug, and drug formulation must be considered.

STUDY QUESTIONS

Choose the ONE best answer.

38.1 Which of the following is a fully human monoclonal antibody?

A. Alemtuzumab
B. Belimumab
C. Eculizumab

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D. Rituximab

Correct answer = B. Infixes (a formative element inserted in a word) are used to indicate the category of monoclonal antibody (-mab). The infix -u- indicates a fully human monoclonal antibody (belimumab), -zu- indicates a humanized monoclonal antibody (alemtuzumab and eculizumab), and -xi- indicates a chimeric monoclonal antibody (rituximab). The immunogenicity of the monoclonal antibodies from least to greatest is fully human < humanized < chimeric.

38.2 A 45-year-old woman needs a renal transplant due to sequela related to chronic hypertension and diabetes. Which of the following agents is most appropriate to include in the induction regimen for this patient?

A. Azathioprine
B. Basiliximab
C. Bortezomib
D. Cyclosporine

Correct answer = B. Basiliximab is a monoclonal antibody used in induction. Cyclosporine and azathioprine are indicated for maintenance therapy, and bortezomib can be used for antibody-mediated organ rejection.

38.3 Which of the following best describes the mechanism of action of cyclosporine?

A. Calcineurin inhibitor
B. Costimulation blocker
C. mTOR inhibitor
D. Antiproliferative

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Correct answer = A. Cyclosporine and tacrolimus are calcineurin inhibitors that block signal transduction through the calcium–calcineurin pathway, activated downstream of signal 1, to impair T-cell activation. Belatacept is a costimulation blocker. mTOR inhibitors include everolimus and sirolimus. Antiproliferatives include mycophenolate and azathioprine.

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38.4 Which of the following immunosuppressant drugs binds to CD52 receptors, resulting in T- and B-cell depletion?

A. Alemtuzumab
B. Belatacept
C. Belimumab
D. Rituximab

Correct answer = A. As a humanized monoclonal antibody, alemtuzumab selectively binds CD52, which is highly expressed on lymphocytes and causes the depletion of both T and B cells from circulation. Rituximab binds the CD20 and can result in B-cell depletion. Belatacept is a selective T-cell costimulatory blocker, while belimumab is a B lymphocyte–specific inhibitor.

38.5 A 29-year-old woman presents to her physician with complaints of heartburn, weight gain, and mood changes after starting a new medication for transplant maintenance. A laboratory evaluation also reveals that her blood glucose is elevated. Which of the following medications most likely caused these adverse effects?

A. Cyclosporine
B. Prednisone
C. Sirolimus
D. Tofacitinib

Correct answer = B. Common adverse effects of corticosteroids (prednisone) can include upset stomach, weight gain, acne, insomnia, hyperglycemia, and mood changes. Patients should be encouraged to take corticosteroids with food and in the morning whenever possible to minimize both stomach distress and trouble sleeping.

38.6 A 44-year-old man presents to his transplant physician for a follow-up appointment. On exam, the patient is hypertensive and has a tremor in both hands. He also complains of a headache. Laboratory evaluation shows an elevated serum

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creatinine. Which of the following medications most likely caused these adverse effects?

A. IVIG
B. Methylprednisolone
C. Rituximab
D. Tacrolimus

Correct answer = D. Tacrolimus requires close therapeutic drug monitoring. Adverse effects of tacrolimus may include increased blood pressure, headache, and tremor. In addition, tacrolimus is nephrotoxic. These effects are more likely when the drug level is above the therapeutic range. The other drugs do not commonly cause these adverse effects.

38.7An 18-year-old woman who received a kidney transplant 6 months prior presents to the transplant clinic complaining of facial hair growth. Her current maintenance regimen includes cyclosporine, mycophenolate mofetil, and prednisone. Which treatment option would be the most appropriate recommendation to address her concerns?

A. Stop mycophenolate mofetil.
B. Stop prednisone and add tofacitinib.
C. Switch cyclosporine to tacrolimus.
D. Switch mycophenolate mofetil to mycophenolic acid.

Correct answer = C. Switch cyclosporine to tacrolimus. Hirsutism, or excessive hair growth, is a well-known adverse effect of cyclosporine. Many patients experience dark, coarse facial or body hair growth while taking cyclosporine. Switching cyclosporine to tacrolimus would eliminate this adverse effect and keep the patient on a calcineurin inhibitor that is effective in preventing rejection. Mycophenolate, tacrolimus, and prednisone are not known to cause hirsutism.

38.8A 45-year-old man who received a renal transplant 3 months ago is being maintained on tacrolimus, prednisone, and mycophenolate mofetil. Findings indicate increased creatinine levels, and a kidney biopsy indicates severe

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rejection. Which additional agent would most likely be appropriate to add at this time?

A. Antithymocyte globulin
B. Azathioprine
C. Basiliximab
D. Methylprednisolone

Correct answer = A. This patient is undergoing an acute rejection of the kidney. The most effective treatment would be administration of an antibody, such as antithymocyte globulin. Azathioprine is an antiproliferative and has no added benefit over mycophenolate mofetil. Basiliximab is often used in combination with other immunosuppressants to prevent organ rejection, but not for the treatment of acute rejection. Methylprednisolone may have some effect but would not be enough to treat the rejection, and this agent would not be added since the patient is already on prednisone.

38.9 Which of the following combinations of immunosuppressive drugs should be avoided?

A. Azathioprine, prednisone, and sirolimus
B. Basiliximab, belatacept, everolimus, and prednisolone
C. Cyclosporine, prednisone, and tacrolimus
D. Everolimus, mycophenolate mofetil, and tacrolimus

Correct answer = C. Tacrolimus and cyclosporine are both calcineurin inhibitors and have the same mechanism of action. Immunosuppressive drug regimens should work synergistically at different places in the T-cell activation cascade. Additionally, cyclosporine and tacrolimus are both extremely nephrotoxic and when used together would cause harm to patients. All of the other combinations are reasonable.

38.10 Which of the following immunosuppressant medications avoids the need for therapeutic drug monitoring?

A. Cyclosporine
B. Tacrolimus
C. Mycophenolate mofetil

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D. Sirolimus

Correct answer = C. Calcineurin inhibitors (cyclosporine and tacrolimus) and mTOR inhibitors (sirolimus and everolimus) require therapeutic drug monitoring in order to maximize efficacy (prevent rejection episodes) and minimize toxicity (adverse effects). Mycophenolate mofetil is the correct answer since there is no role for routine monitoring with this medication.

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Unit VII:
Special Topics in Pharmacology

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39

Histamine and Serotonin

Nancy Borja-Hart

I. OVERVIEW

Histamine and serotonin, along with prostaglandins, belong to a group of endogenous compounds called autacoids. These heterogeneous substances have widely differing structures and pharmacologic activities. They all have the common feature of being formed by the tissues on which they act and, therefore, function as local hormones. [Note: The word "autacoid" comes from the Greek: *autos* (self) and *akos* (medicinal agent, or remedy).] The autacoids also differ from circulating hormones in that they are produced by many tissues rather than in specific endocrine glands. The drugs described in this chapter are either autacoids or autacoid antagonists (compounds that inhibit the synthesis of certain autacoids or that interfere with their interactions with receptors). This chapter reviews the histamine H_1-receptor antagonists (antihistamines), and it provides an overview of serotonin agonists used in the treatment and prevention of migraine.

Pharmacy Drug

II. HISTAMINE

Histamine is a chemical messenger mostly generated in mast cells. Histamine, via multiple receptor systems, mediates a wide range of cellular responses, including allergic and inflammatory reactions, gastric acid secretion, and neurotransmission in parts of the brain. Histamine has no clinical applications, but agents that inhibit the

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action of histamine (antihistamines or histamine receptor blockers) have important therapeutic applications. Figure 39.1 provides a summary of the H_1-receptor antagonists (antihistamines).

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H1 ANTIHISTAMINES

Alcaftadine LASTACAFT
Azelastine ASTEPRO
Bepotastine BEPREVE
Brompheniramine BROMAX, LO-HIST
Cetirizine ZYRTEC
Chlorpheniramine GENERIC ONLY
Clemastine GENERIC ONLY
Cyproheptadine GENERIC ONLY
Desloratadine CLARINEX
Dimenhydrinate DRAMAMINE
Diphenhydramine BENADRYL
Doxylamine UNISOM
Fexofenadine ALLEGRA
Hydroxyzine VISTARIL
Ketotifen ALAWAY, ZADITOR
Levocetirizine XYZAL
Loratadine CLARITIN
Meclizine ANTIVERT
Olopatadine PATADAY, PATANASE
Promethazine PHENERGAN

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Figure 39.1 Summary of antihistamines.

A. Location, synthesis, and release of histamine

1. Location: Histamine is present in practically all tissues, with significant amounts in the lungs, skin, blood vessels, and gastrointestinal (GI) tract. It is found in high concentrations in mast cells and basophils. Histamine functions as a neurotransmitter in the brain. It also occurs as a component of venoms and in secretions from insect stings.

2. Synthesis: Histamine is an amine formed by the decarboxylation of the amino acid histidine by the enzyme histidine decarboxylase, which is expressed in cells throughout the body, including neurons, gastric parietal cells, mast cells, and basophils (Figure 39.2). In mast cells, histamine is stored in granules. If histamine is not stored, it is rapidly inactivated by the enzyme amine oxidase.

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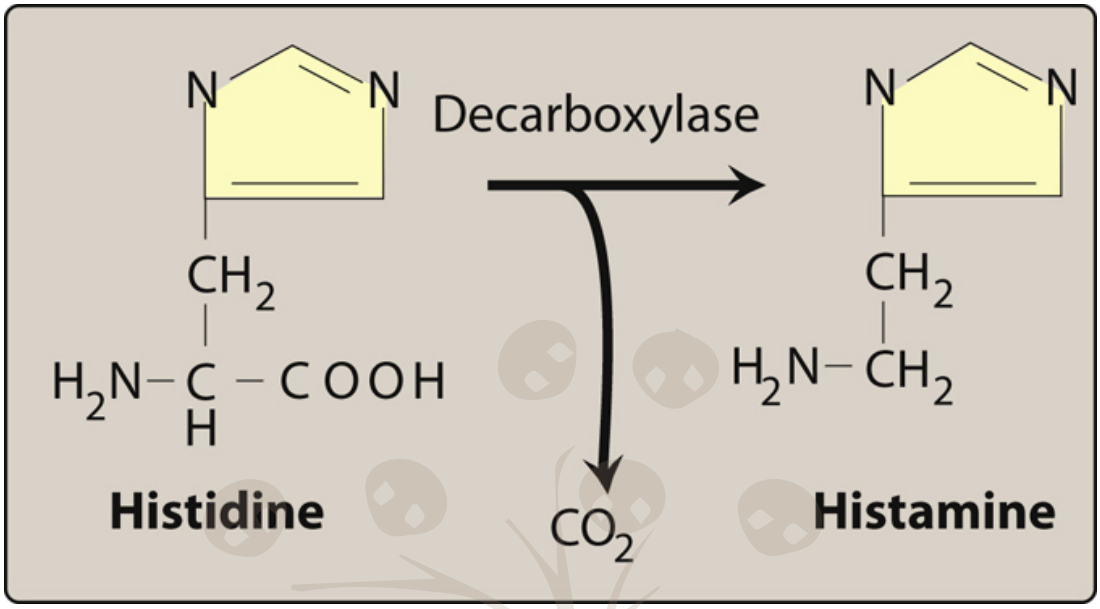

Figure 39.2 Biosynthesis of histamine.

3. Release of histamine: Most often, histamine is just one of the several chemical mediators released in response to stimuli. The stimuli for release of histamine from tissues may include destruction of cells as a result of cold, toxins from organisms, venoms from insects and spiders, and trauma. Allergies and anaphylaxis can also trigger significant release of histamine.

B. Mechanism of action

Histamine released in response to certain stimuli exerts its effects by binding to various types of histamine receptors. H_1 and H_2 receptors are widely expressed and are the targets of clinically useful drugs. Histamine has a wide range of pharmacologic effects that are mediated by both H_1 and H_2 receptors. For example, the H_1 receptors are important in producing smooth muscle contraction and increasing capillary permeability (Figure 39.3). Histamine promotes vasodilation of small blood vessels by causing the vascular endothelium to release nitric oxide. In addition, histamine can enhance the secretion of proinflammatory

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cytokines in several cell types and in local tissues. Histamine H_1 receptors mediate many pathological processes, including allergic rhinitis, atopic dermatitis, conjunctivitis, urticaria, bronchoconstriction, asthma, and anaphylaxis. Moreover, histamine stimulates the parietal cells in the stomach, causing an increase in acid secretion via the activation of H_2 receptors (see Chapter 42).

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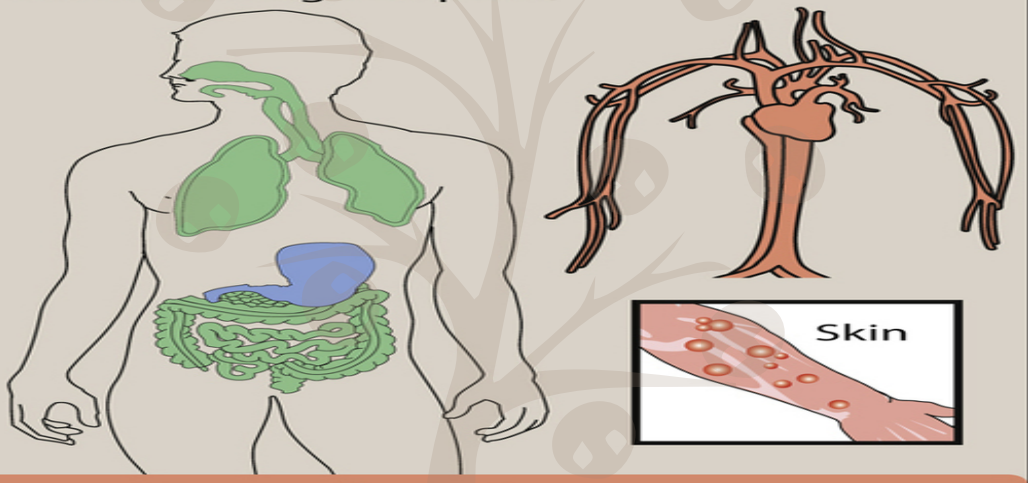
H_1 Receptors

Exocrine excretion
Increased production of nasal and bronchial mucus, resulting in respiratory symptoms.

Bronchial smooth muscle
Constriction of bronchioles results in symptoms of asthma and decreased lung capacity.

Intestinal smooth muscle
Constriction results in intestinal cramps and diarrhea.

Sensory nerve endings
Causes itching and pain.



H_1 and H_2 Receptors

Cardiovascular system
Lowers systemic blood pressure by reducing peripheral resistance. Causes positive chronotropism (mediated by H_2 receptors) and a positive inotropism (mediated by both H_1 and H_2 receptors).

Skin
Dilation and increased permeability of the capillaries results in leakage of proteins and fluid into the tissues. In the skin, this results in the classic "triple response": wheal formation, reddening due to local vasodilation, and flare ("halo").

H_2 Receptors

Stomach
Stimulation of gastric hydrochloric acid secretion.

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Figure 39.3 Actions of histamine.

C. Role in allergy and anaphylaxis

The symptoms resulting from intravenous injection of histamine are similar to those associated with anaphylactic shock and allergic reactions. These include contraction of airway smooth muscle, stimulation of secretions, dilation and increased permeability of the capillaries, and stimulation of sensory nerve endings. Symptoms associated with allergy and anaphylactic shock result from the release of certain mediators from their storage sites. Such mediators include histamine, serotonin, leukotrienes, and the eosinophil chemotactic factor of anaphylaxis. In some cases, these mediators cause a localized allergic reaction, producing, for example, actions on the skin or respiratory tract. Under other conditions, these mediators may cause a full-blown anaphylactic response. It is thought that the difference between these two situations results from differences in the sites from which mediators are released and in their rates of release. For example, if the release of histamine is slow enough to permit its inactivation before it enters the bloodstream, it likely results in a local allergic reaction. However, if histamine release is too fast for efficient inactivation, a full-blown anaphylactic reaction occurs.

III. HISTAMINE H_1-RECEPTOR BLOCKERS (ANTIHISTAMINES)

The term “antihistamine” refers primarily to the classic H_1-receptor blockers. The H_1-receptor blockers can be divided into first-generation and second-generation drugs (Figure 39.4). The older first-generation drugs are still widely used because they are effective and inexpensive. However, most of these drugs penetrate the central

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nervous system (CNS) and cause sedation. Furthermore, they tend to interact with other receptors, producing a variety of unwanted adverse effects. By contrast, the second-generation agents are specific for peripheral H_1 receptors. The second-generation antihistamines are made polar, mainly by adding carboxyl groups (for example, *cetirizine* is the carboxylated derivative of *hydroxyzine*), and, therefore, these agents do not penetrate the blood–brain barrier and cause less CNS depression than do the first-generation drugs. Among the second-generation agents, *desloratadine* [des-lor-AH-tah-deen], *fexofenadine* [fex-oh-FEN-a-deen], and *loratadine* [lor-AT-a-deen] show the least sedation (Figure 39.5). *Cetirizine* [seh-TEER-ih-zeen] and *levocetirizine* [lee-voe-seh-TEER-ih-zeen] are partially sedating second-generation agents.

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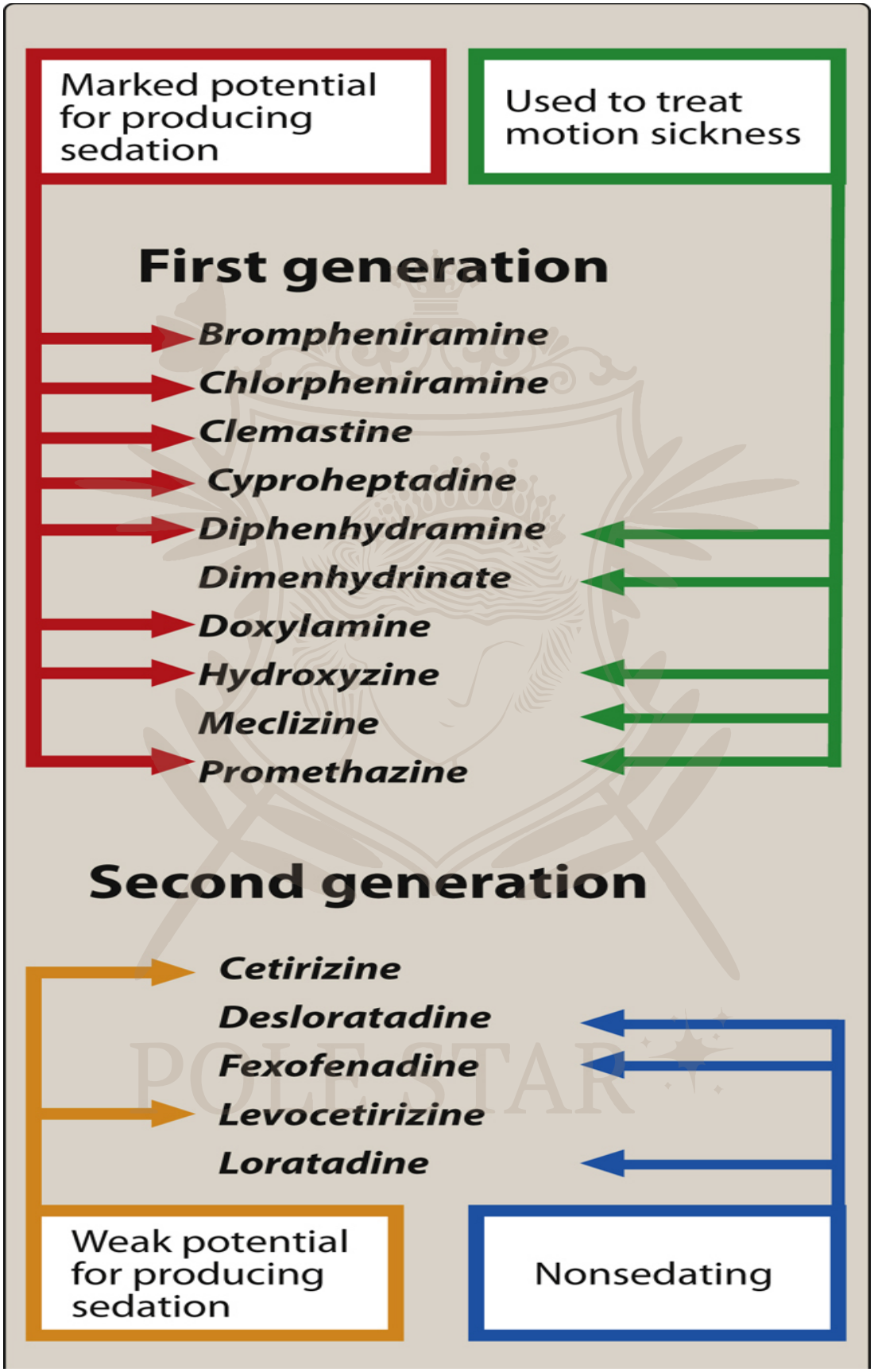
Marked potential for producing sedation
Used to treat motion sickness
First generation
Brompheniramine
Chlorpheniramine
Clemastine
Cyproheptadine
Diphenhydramine
Dimenhydrinate
Doxylamine
Hydroxyzine
Meclizine
Promethazine
Second generation
Cetirizine
Desloratadine
Fexofenadine
Levocetirizine
Loratadine
Weak potential for producing sedation
Nonsedating

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Figure 39.4 Summary of therapeutic advantages and disadvantages of some H_1 histamine receptor–blocking agents.

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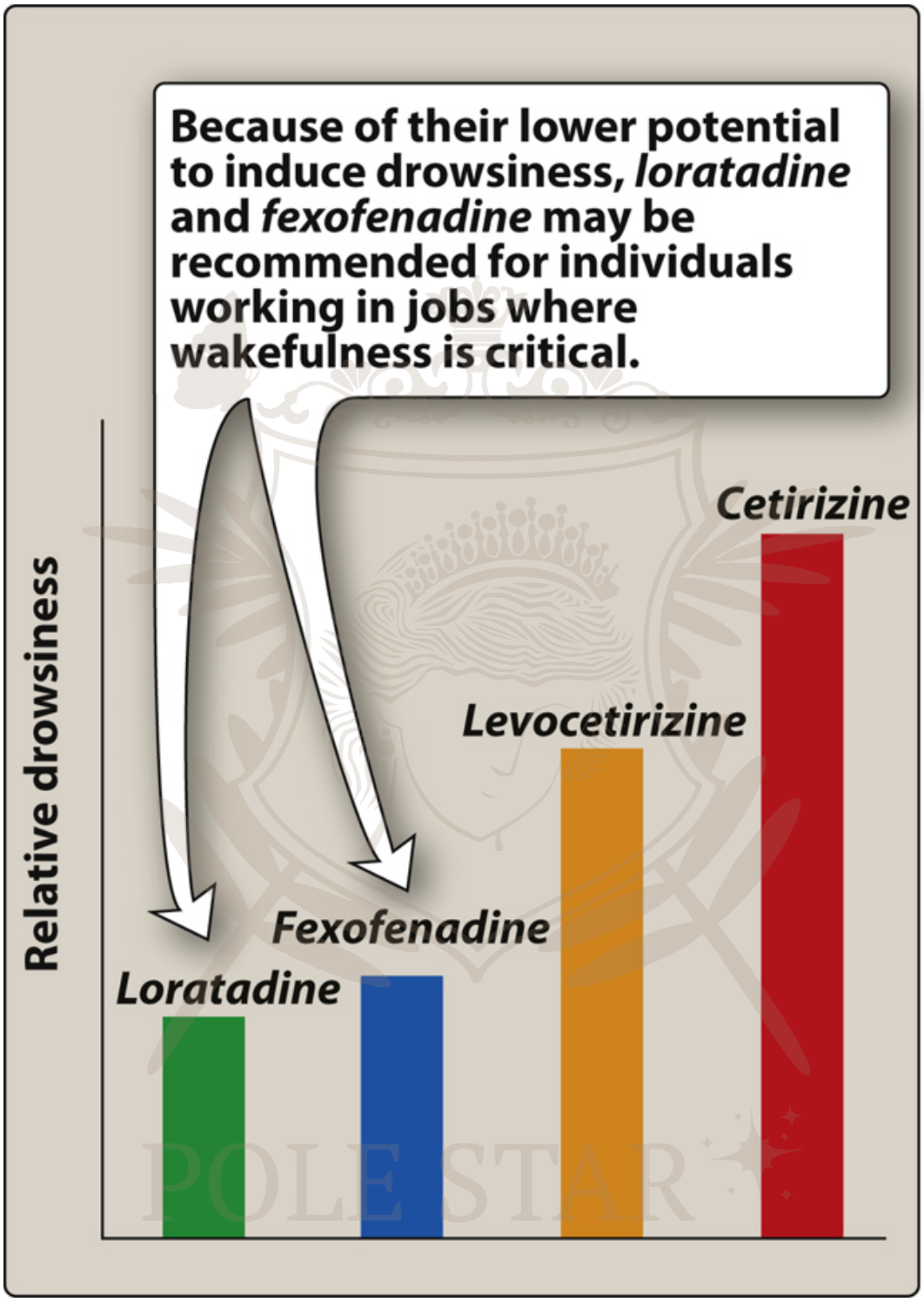

Figure 39.5 Relative potential for drowsiness with second-generation H_1 antihistamines.

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A. Actions

The action of all H_1-receptor blockers is qualitatively similar. Most of these compounds do not influence the formation or release of histamine. Rather, they block the receptor-mediated response of a target tissue. They are much more effective in preventing symptoms than reversing them once they have occurred. However, most of these agents have additional effects unrelated to their ability to block H_1 receptors. These effects reflect binding of the H_1-receptor antagonists to cholinergic, adrenergic, or serotonin receptors (Figure 39.6). For example, *cyproheptadine* [SYE-proe-HEP-ta-deen] also acts as a serotonin antagonist and can be used for appetite stimulation or the management of serotonin syndrome. Antihistamines such as *azelastine* [a-ZEL-uh-steen] and *ketotifen* [kee-toe-TYE-fen] also have mast cell–stabilizing effects in addition to their histamine receptor–blocking effects.

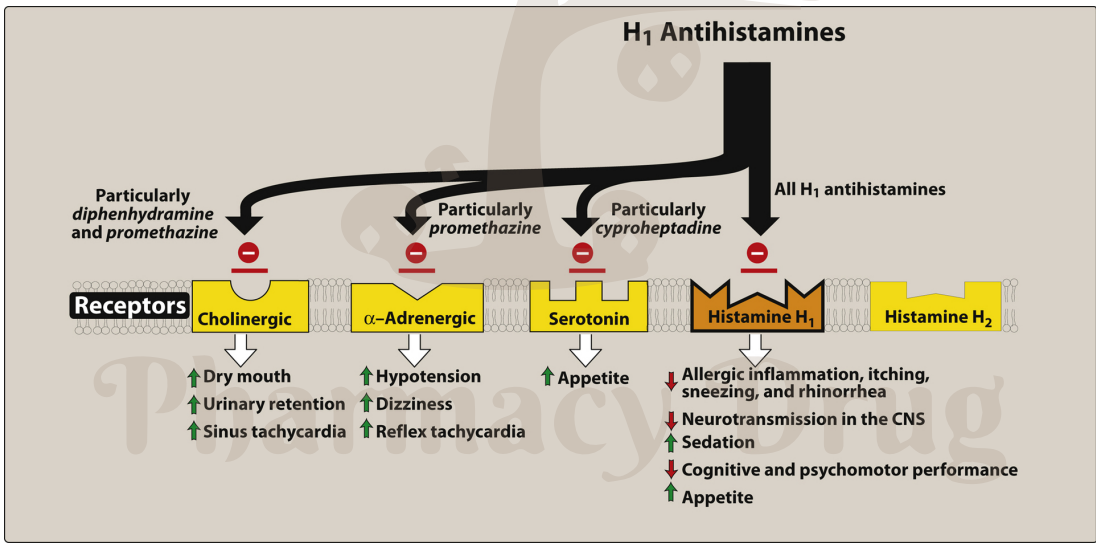

Figure 39.6 Effects of H_1 antihistamines at histamine, adrenergic, cholinergic, and serotonin-binding receptors.CNS = central nervous system.

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B. Therapeutic uses

1. Allergic and inflammatory conditions: H_1-receptor blockers are useful in treating and preventing allergic reactions caused by antigens acting on immunoglobulin E antibody. For example, oral antihistamines are the drugs of choice in controlling the symptoms of allergic rhinitis and urticaria because histamine is the principal mediator released by mast cells. Ophthalmic antihistamines, such as *azelastine*, *olopatadine* [oh-loe-PAT-a-deen], *ketotifen*, and others, are useful for the treatment of allergic conjunctivitis. However, the H_1-receptor blockers are not indicated in treating bronchial asthma, because histamine is only one of the several mediators that are responsible for causing bronchial reactions. [Note: *Epinephrine* has actions on smooth muscle that are opposite to those of histamine. It acts via β_2 receptors on smooth muscle, causing cAMP-mediated relaxation. Therefore, *epinephrine* is the drug of choice in treating systemic anaphylaxis and other conditions that involve massive release of histamine.]

Clinical Application 39.1 Management of Allergic Rhinitis

The hallmark symptoms of allergic rhinitis include nasal congestion, rhinorrhea, itching, and sneezing. Antihistamines do not help with nasal congestion, but they do target the other three symptoms and are useful therapeutic agents for the management of allergic rhinitis. Intranasal corticosteroids (see Chapter 41) are the most effective medications available for allergic rhinitis due to their ability to manage all of the hallmark symptoms.

2. Motion sickness and nausea: Along with the antimuscarinic agent *scopolamine*, certain H_1-receptor blockers, such as *diphenhydramine* [dye-fen-HYE-dra-meen], *dimenhydrinate* [dye-men-HYE-dri-nate] (a chemical combination of *diphenhydramine* and a chlorinated *theophylline* derivative), *meclizine* [MEK-li-zeen], and

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promethazine [proe-METH-a-zeen], are the most effective agents for prevention of the symptoms of motion sickness. They are usually not effective if symptoms are already present and, thus, should be taken prior to expected travel. The antihistamines prevent or diminish nausea and vomiting mediated by both the chemoreceptor and vestibular pathways. The antiemetic action of these medications seems to be due to their blockade of central H_1 and M_1 muscarinic receptors. *Meclizine* is also useful for the treatment of vertigo associated with vestibular disorders.

3. Insomnia: Although they are not the medications of choice, many first-generation antihistamines, such as *diphenhydramine* and *doxylamine* [dox-IL-a-meen], have strong sedative properties and are used in the treatment of insomnia. First-generation H_1 antihistamines must be used with caution in the treatment of individuals working in jobs in which wakefulness is critical. The second-generation antihistamines have no value for inducing sleep.

C. Pharmacokinetics

H_1-receptor blockers are well absorbed after oral administration, with maximum serum levels occurring at 1 to 2 hours. The average duration of action is 4 to 6 hours, except for that of *meclizine* and the second-generation agents, which is 12 to 24 hours, allowing for once-daily dosing. First-generation H_1-receptor blockers are distributed in all tissues, including the CNS. All first-generation H_1 antihistamines and some second-generation H_1 antihistamines, such as *desloratadine* and *loratadine*, are metabolized by the hepatic cytochrome P450 system. *Levocetirizine* is the active enantiomer of *cetirizine. Cetirizine* and *levocetirizine* are excreted largely unchanged in urine, and *fexofenadine* is excreted largely unchanged in feces. After a single oral dose, the onset of action occurs within 1 to 3 hours. *Azelastine*, *olopatadine*, *ketotifen*, *alcaftadine* [al-KAF-ta-deen],

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and *bepotastine* [bep-oh-TAS-teen] are available in ophthalmic formulations that allow for more targeted tissue delivery. *Azelastine* and *olopatadine* have intranasal formulations, as well.

D. Adverse effects

First-generation H_1-receptor blockers have a low specificity, interacting not only with histamine receptors but also with muscarinic cholinergic receptors, α-adrenergic receptors, and serotonin receptors (Figure 39.6). The extent of interaction with these receptors and, as a result, the nature of the adverse effects vary with the structure of the drug. Some side effects may be undesirable, and others may be of therapeutic value. Furthermore, the incidence and severity of adverse reactions for a given drug varies between individual subjects.

1. Sedation: First-generation H_1 antihistamines, such as *chlorpheniramine* [klor-fen-IR-a-meen], *diphenhydramine*, *hydroxyzine* [hye-DROX-ee-zeen], and *promethazine*, bind to H_1 receptors and block the neurotransmitter effect of histamine in the CNS. The most frequently observed adverse reaction is sedation (Figure 39.7); however, *diphenhydramine* may cause paradoxical hyperactivity in young children. Other central actions include fatigue, dizziness, lack of coordination, and tremors. Elderly patients are more sensitive to these effects. Sedation is less common with the second-generation drugs, since they do not readily enter the CNS. Second-generation H_1 antihistamines are specific for peripheral H_1 receptors.

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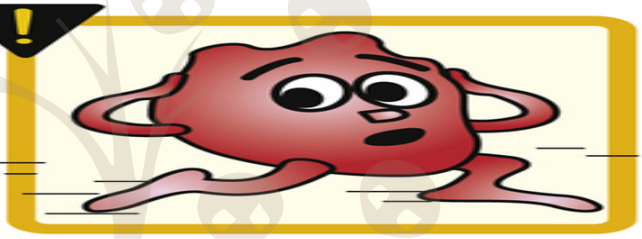
Drowsiness

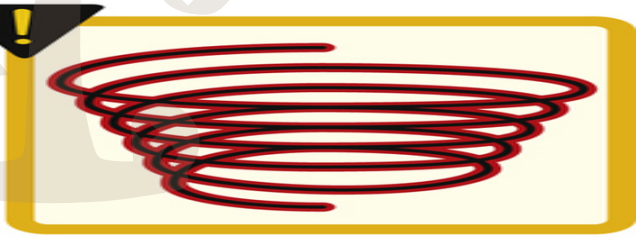
Urinary retention

Tachycardia

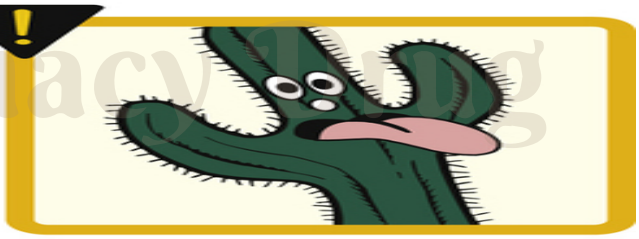


Hypotension

Vertigo



Dry mouth



Increased appetite

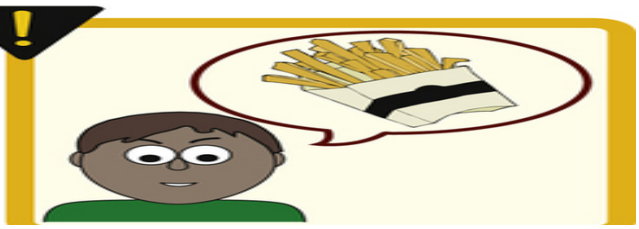


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Figure 39.7 Some adverse effects observed with antihistamines.BP = blood pressure.

2.Other effects: First-generation antihistamines exert anticholinergic effects, leading to dryness in the nasal passage and oral cavity. They may also cause blurred vision and retention of urine. The most common adverse reaction associated with second-generation antihistamines is headache. Topical formulations of *diphenhydramine* can cause local hypersensitivity reactions such as contact dermatitis.

3.Drug interactions: Interaction of H_1-receptor blockers with other drugs can cause serious consequences, such as potentiation of effects of other CNS depressants, including alcohol. Patients taking monoamine oxidase inhibitors (MAOIs), such as *phenelzine*, should not take antihistamines because the MAOIs can exacerbate the sedative and anticholinergic effects of antihistamines. In addition, the first-generation antihistamines (*diphenhydramine* and others) with anticholinergic (antimuscarinic) actions may decrease the effectiveness of cholinesterase inhibitors (*donepezil*, *rivastigmine*, and *galantamine*) in the treatment of Alzheimer disease.

4.Overdose: Although the margin of safety of H_1-receptor blockers is relatively high and chronic toxicity is rare, acute poisoning does occur, especially in young children. The most common and dangerous effects of acute poisoning are those on the CNS, including hallucinations, excitement, ataxia, and convulsions. If untreated, the patient may experience a deepening coma and collapse of the cardiorespiratory system.

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IV. HISTAMINE H_2-RECEPTOR BLOCKERS

Histamine H_2-receptor blockers have little, if any, affinity for H_1 receptors. Although antagonists of the histamine H_2 receptor (H_2 antagonists or H_2-receptor blockers) block the actions of histamine at all H_2 receptors, the primary clinical use is as inhibitors of gastric acid secretion in the treatment of ulcers and heartburn. The H_2-receptor blockers *cimetidine*, *famotidine*, and *nizatidine* are discussed in Chapter 42.

V. SEROTONIN

Serotonin is a neurotransmitter within the enteric nervous system and the CNS. It plays a role in vasoconstriction, inhibition of gastric secretion, and stimulation of smooth muscle contraction. Within the GI tract, it may serve as a local hormone to influence GI motility and secretion. Within the brain, the serotonergic neurons affect mood, appetite, body temperature regulation, and sleep. While serotonin has no direct clinical application, agents that activate its receptor subtypes or antagonize its actions do have clinical utility in the management of several disorders, such as depression and migraine headache.

A. Location, synthesis, and release of serotonin

1. Location: Serotonin is largely present within the enterochromaffin cells of the GI tract. It is also found in storage granules in platelets and the raphe nuclei of the brainstem.

2. Synthesis: Serotonin (also known as 5-hydroxytryptamine, 5-HT) is synthesized from the amino acid l-tryptophan. l-Tryptophan undergoes hydroxylation of the indole ring to form l-5-hydroxytryptophan, followed by decarboxylation to form 5-hydroxytryptamine.

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3.Release of serotonin: Following synthesis, serotonin is stored in vesicles and is released by exocytosis of the vesicle in response to an action potential. The activity of serotonin is terminated by uptake into the neuron and platelets. Metabolism occurs mainly via monoamine oxidase.

B. Mechanism of action

There are several families of 5-HT receptors designated by numeric subscripts. Most of these are G protein–coupled receptors, while the 5-HT_3 receptor is a ligand-gated cation channel. The 5-HT_1 and 5-HT_2 receptors have several subtypes denoted by letters (for example, 5-HT_{2C}). Serotonin has a wide range of effects that are mediated by the different types of serotonin receptors. For example, serotonin activity at 5-HT_{2C} receptors in the CNS may cause a reduction in appetite, and stimulation of 5-HT_3 receptors in the GI tract and vomiting center may trigger emesis. [Note: 5-HT_3 receptor antagonists are highly effective for the management of chemotherapy-induced or postsurgical nausea and vomiting; see Chapter 42.]

C. Therapeutic uses

Selective serotonin agonists have a variety of clinical indications, depending on the receptor specificity. Serotonin has a role in the pathophysiology of clinical depression, and agents such as selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are effective therapies for this condition (see Chapter 17). The clinical use of serotonin agonists in the management of migraine is further described below.

VI. DRUGS USED TO TREAT HEADACHE DISORDERS

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The most common types of headaches are migraine, tension-type, and cluster headaches. Migraines can usually be distinguished from cluster headaches and tension-type headaches by the characteristics shown in Figure 39.8. Patients with severe migraine headaches report one to five attacks per month of moderate to severe pain, which is usually unilateral. Headache disorders significantly affect quality of life and result in considerable healthcare costs. Management of headaches involves avoidance of headache triggers (for example, alcohol, chocolate, and stress) and use of abortive treatments for acute headaches, as well as prophylactic therapy in patients with frequent or severe migraines (Figure 39.9).

	MIGRAINE	CLUSTER	TENSION TYPE
Family history	Yes	No	Yes
Sex	Females more often than males	Males more often than females	Females more often than males
Onset	Variable	During sleep	Under stress
Location	Usually unilateral	Behind or around one eye	Bilateral in band around head
Character and severity	Pulsating, throbbing	Excruciating, sharp, steady	Dull, persistent, tightening
Duration	2–72 hours per episode	15–90 minutes per episode	30 minutes to 7 days per episode
Associated symptoms	Visual auras, sensitivity to light and sound, pale facial appearance, nausea and vomiting	Unilateral or bilateral sweating, facial flushing, nasal congestion, lacrimation, pupillary changes	Mild intolerance to light and noise, anorexia

Figure 39.8 Characteristics of migraine, cluster, and tension-type headaches.Data from D. D.Dubose , A. C.Cutlip , and W. D.Cutlip . Migraines and other headaches: an approach to diagnosis and classification. *Am. Fam. Physician*. 51: 1498 (1995).

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TRIPTANS

Almotriptan GENERIC ONLY
Eletriptan RELPAX
Frovatriptan FROVA
Naratriptan AMERGE
Rizatriptan MAXALT, MAXALT-MLT
Sumatriptan IMITREX, ONZETRA, ZEMBRACE
Zolmitriptan ZOMIG

ERGOTS

Dihydroergotamine DHE 45, MIGRANAL
Ergotamine tartrate ERGOMAR

DITANS

Lasmiditan REYVOW

CGRP RECEPTOR ANTAGONISTS

Rimegepant NURTEC
Ubrogepant UBRELVY

NSAIDs

Aspirin BAYER, BUFFERIN, ECOTRIN
Ibuprofen ADVIL, MOTRIN
Indomethacin INDOCIN
Ketorolac GENERIC ONLY
Naproxen ALEVE, ANAPROX, NAPROSYN

PROPHYLACTIC AGENTS

Anticonvulsants
Antidepressants
β-Blockers
Calcium channel blockers
CGRP antagonists
OnabotulinumtoxinA BOTOX

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Figure 39.9 Summary of drugs used to treat migraine headache.CGRP = calcitonin gene–related peptide.

Clinical Application 39.2: Types of Migraine

There are two main types of migraine headaches. The first, migraine without aura, is a severe, unilateral, pulsating headache that typically lasts from 2 to 72 hours. These headaches are often aggravated by physical activity and are accompanied by nausea, vomiting, photophobia (hypersensitivity to light), and phonophobia (hypersensitivity to sound). The majority of patients with migraine do not have aura. In the second type, migraine with aura, the headache is preceded by neurologic symptoms called auras, which can be visual, sensory, and/or cause speech or motor disturbances. Most commonly, these prodromal symptoms are visual (flashes, zigzag lines, and glare) and occur approximately 20 to 40 minutes before headache pain begins. In the 15% of migraine patients whose headache is preceded by an aura, the aura itself allows diagnosis. The headache in migraines with or without auras is similar. Women are threefold more likely than are men to experience either type of migraine.

A. Biologic basis of migraine headaches

The first manifestation of migraine with aura is a spreading depression of neuronal activity accompanied by reduced blood flow in the most posterior part of the cerebral hemisphere. This hypoperfusion gradually spreads forward over the surface of the cortex to other contiguous areas of the brain. The vascular alteration is accompanied by functional changes. The hypoperfusion persists throughout the aura and well into the headache phase. Patients who have migraine without aura do not show hypoperfusion. However, the pain of both types of migraine may be due to extracranial and intracranial arterial vasodilation, which leads to release of neuroactive molecules, such as substance P, neurokinin A, and calcitonin gene–related peptide (CGRP).

B. Symptomatic treatment of acute migraine

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Acute treatments can be classified as nonspecific (symptomatic) or migraine specific. Nonspecific treatment includes analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs; see Chapter 40) and antiemetics (for example, *prochlorperazine*) to control vomiting. Migraine-specific therapy includes serotonin agonists (for example, triptans, ergot alkaloids, and ditans), as well as CGRP receptor antagonists.

1. Triptans: This class of drugs includes *almotriptan* [al-moe-TRIP-tan], *eletriptan* [el-e-TRIP-tan], *frovatriptan* [froe-va-TRIP-tan], *naratriptan* [nar-a-TRIP-tan], *rizatriptan* [rye-za-TRIP-tan], *sumatriptan* [soo-ma-TRIP-tan], and *zolmitriptan* [zole-ma-TRIP-tan]. *Sumatriptan* was the first available triptan and is the prototype of this class. These agents rapidly and effectively abort or markedly reduce the severity of migraine headaches in about 70% of patients and are first-line agents in the treatment of acute migraine. The triptans are 5-$HT_{1B/1D}$ receptor agonists, acting at a subgroup of serotonin receptors found on small peripheral nerves that innervate the intracranial vasculature. It has been proposed that activation of 5-HT_1 receptors by these agents leads to vasoconstriction and/or inhibition of the release of proinflammatory neuropeptides from the trigeminal nerve system. *Sumatriptan* is given subcutaneously, intranasally, or orally (*sumatriptan* is also available in a combination product with *naproxen*). *Zolmitriptan* is available as an oral tablet or nasal spray. All other agents are taken orally. The onset of the parenteral drug *sumatriptan* is about 20 minutes, compared with 1 to 2 hours when the drug is administered orally. The drug has a short duration of action, with an elimination half-life of 2 hours. Headache commonly recurs within 24 to 48 hours after a single dose of drug, but in most patients, a second dose is effective in aborting the headache. *Frovatriptan* is the longest-acting triptan, with a half-life of more than 24 hours. Individual response to triptans varies, and a trial of more than one triptan may be necessary before treatment is successful. Elevation of

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blood pressure and other cardiac events have been reported with triptan use. Therefore, triptans should not be administered to patients with risk factors for coronary artery disease without performing a cardiac evaluation prior to administration. Other adverse events with the use of triptans include pain and pressure sensations in the chest, neck, throat, and jaw. Dizziness and malaise have also been seen with the use of triptans.

2.Ergot alkaloids: *Ergotamine* [er-GOT-a-meen] and *dihydroergotamine* [dye-hye-droe-er-GOT-a-meen], a semisynthetic derivative of *ergotamine*, are ergot alkaloids approved for the treatment of migraine headaches. The action of the ergot alkaloids is complex, with ability to bind to 5-HT_1 receptors, α receptors, and dopamine receptors. 5-HT_1 receptors located on intracranial blood vessels are targets that cause vasoconstriction with the use of these agents. *Ergotamine* is currently available sublingually and is mostly effective when used in the early stages of the migraine. It is also available as an oral tablet or suppository containing both *ergotamine* and *caffeine. Ergotamine* is used with strict daily and weekly dosage limits due to its ability to cause dependence and rebound headaches. *Dihydroergotamine* is administered intravenously or intranasally and has an efficacy similar to that of *sumatriptan.* The use of *dihydroergotamine* is limited to cases of severe migraine. Nausea is a common adverse effect. *Ergotamine* and *dihydroergotamine* are contraindicated in patients with angina and peripheral vascular disease because they are significant vasoconstrictors. Ergot alkaloids should not be used within 24 hours of triptans due to the risk of coronary ischemia. In addition, potentially life-threatening peripheral ischemia has been associated with the coadministration of these agents with potent CYP3A4 inhibitors.

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3.Ditans: *Lasmiditan* [las-MID-i-tan] is a selective 5-HT_{1F} agonist in the drug class of ditans. The mechanism of action is unknown, but it is thought to reduce activation of the trigeminal nerve system pain pathways. Unlike triptans and ergot alkaloids, this agent does not cause vasoconstriction. *Lasmiditan* is an oral agent indicated for acute treatment of migraine in patients who have contraindications or intolerance to triptans. The drug has a potential for abuse and is classified as a controlled substance. It may cause significant driving impairment, and patients should be advised not to engage in hazardous activities when taking this drug.

4.CGRP receptor antagonists: Calcitonin gene–related peptide receptor antagonists (also known as *gepants*) include *rimegepant* [ri-ME-je-pant] and *ubrogepant* [ue-BROE-je-pant]. CGRP is believed to play a role in the pathophysiology of migraine, and levels of this neuropeptide are elevated in acute migraine. *Rimegepant* and *ubrogepant* are indicated in the treatment of acute migraine in patients with contraindications or intolerance to triptans. These agents are administered orally. [Note: *Rimegepant* and *atogepant* (a-TOE-je-pant), another oral CGRP antagonist, can be used for the prevention of migraine headaches.] The most common adverse effects are nausea and somnolence, although the incidence is low. Concomitant administration of *ubrogepant* with strong CYP3A4 inhibitors is contraindicated.

C. Prophylaxis for migraine headache

POLE STAR

Therapy to prevent migraine is indicated if the attacks occur two or more times a month and if the headaches are severe or complicated by serious neurologic signs. β-Blockers (*propranolol*, *metoprolol*) are the drugs of choice for migraine prophylaxis; however, calcium channel blockers (*verapamil*), anticonvulsants (*topiramate* and *divalproex*), antidepressants (*amitriptyline, venlafaxine*), and *onabotulinumtoxin A* may be used. In addition, the oral CGRP antagonists *rimegepant* and *atogepant* and

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injectable monoclonal antibodies that are CGRP antagonists (for example, *erenumab*, *galcanezumab*, *fremanezumab*, and *eptinezumab*) have also shown effectiveness in migraine prevention (Figure 39.10).

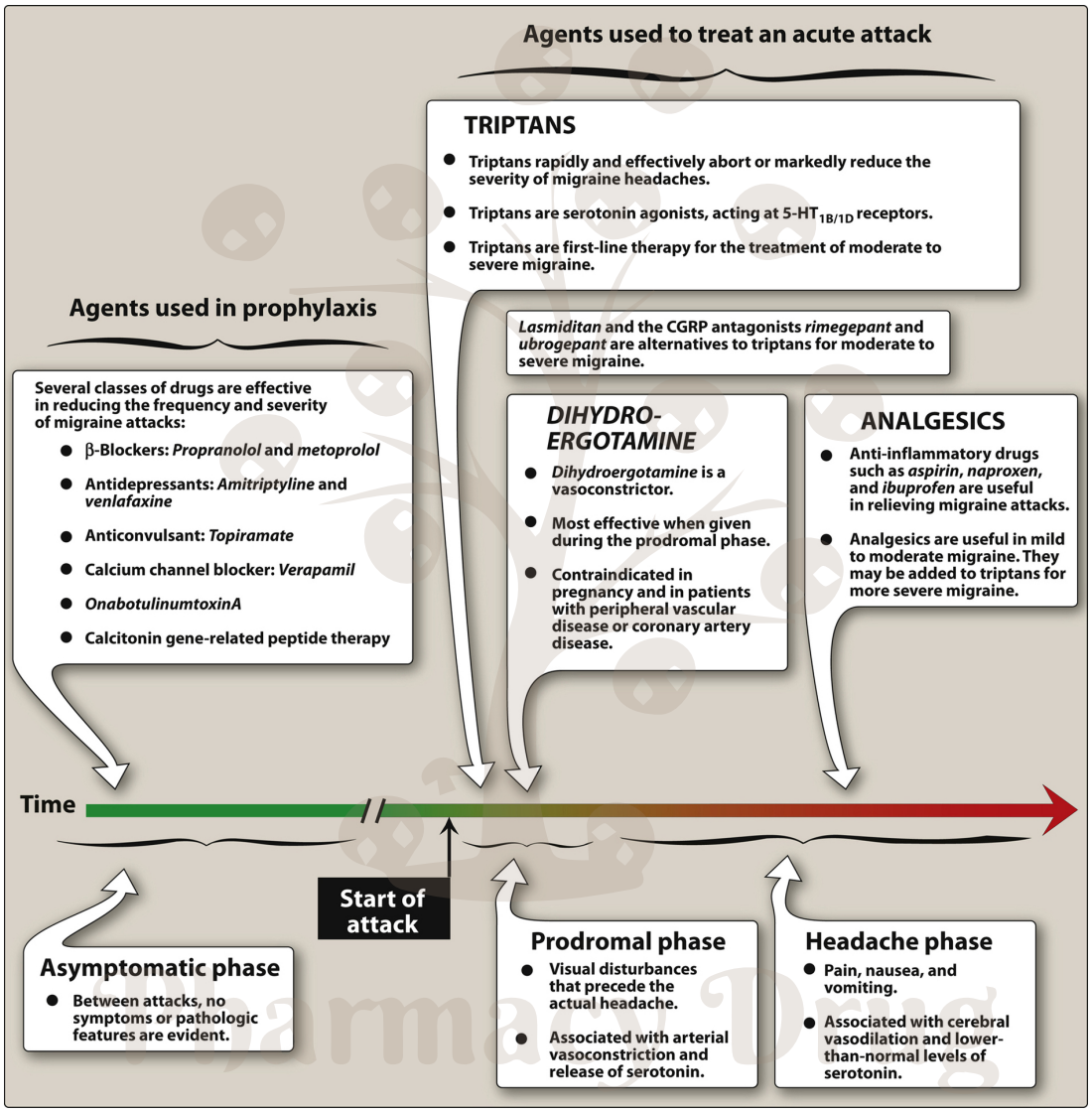

Figure 39.10 Drugs used in the treatment and prophylaxis of migraine headaches.CGRP = calcitonin gene–related peptide.

D. Drugs for tension and cluster headache

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Analgesics (NSAIDS, *acetaminophen*, *aspirin*) are used for symptom relief of tension headaches, with NSAIDs as the preferred therapy. Triptans, along with inhalation of 100% oxygen, are used as first-line abortive strategies for cluster headache.

Chapter Summary

- Histamine mediates a wide range of cellular responses, including allergic and inflammatory reactions, gastric acid secretion, and neurotransmission in parts of the brain.
- Antihistamine refers primarily to the classic H_1-receptor blockers, which are useful in preventing and treating common symptoms related to allergies, such as rhinorrhea, sneezing, and hives.
- First-generation antihistamines, such as *chlorpheniramine*, *diphenhydramine*, and *hydroxyzine*, can cause adverse effects such as sedation, dizziness, blurred vision, and urinary retention. Second-generation agents, such as *fexofenadine*, *loratadine*, and *cetirizine*, are less likely to cause sedation, but may cause headache.
- Serotonin is a neurotransmitter which plays a role in vasoconstriction, inhibition of gastric secretion, and stimulation of smooth muscle contraction.
- Serotonin agonists (triptans, ergot alkaloids, and ditans) are effective as abortive agents in the acute treatment of migraine headache.
- Triptans are first-line therapy for moderate to severe migraine. These agents can cause an elevation of blood pressure and should not be given to patients with risk factors for coronary artery disease without an appropriate cardiac evaluation.
- *Ergotamine* and *dihydroergotamine* are significant vasoconstrictors, and they are contraindicated in patients with angina and peripheral vascular disease.
- The CGRP antagonists *rimegepant* and *ubrogepant* may be used in the acute treatment of migraine in patients who have contraindications or intolerance to triptans.

POLE STAR

STUDY QUESTIONS

Choose the ONE best answer.

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39.1 Which histamine receptor antagonist is known to enter the central nervous system readily and cause sedation?

A. Hydroxyzine
B. Cetirizine
C. Desloratadine
D. Loratadine

Correct answer = A. Choices B, C, and D are all second-generation antihistamines that cross the blood–brain barrier to a much lesser extent than does hydroxyzine. Hydroxyzine is the only drug that crosses the blood–brain barrier easily.

39.2 Which of the following drugs is an H_1-receptor antagonist that also has serotonin receptor antagonism on the appetite center, with the ability to stimulate appetite?

A. Hydroxyzine
B. Loratadine
C. Diphenhydramine
D. Cyproheptadine

Correct answer = D. Cyproheptadine has significant serotonin antagonism and is known to increase appetite.

39.3 A 43-year-old man presents to his physician with complaints of seasonal allergies. He is a heavy machine operator. Which medication is the most appropriate for the management of his allergy symptoms?

A. Diphenhydramine
B. Doxylamine
C. Hydroxyzine
D. Fexofenadine

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Correct answer = D. First-generation H_1 antihistamines should be avoided in the treatment of individuals who must remain alert, such as those that operate heavy machinery. For example, because of their adverse effects, they are not approved for use by pilots. Because of its lower potential to induce drowsiness, fexofenadine may be recommended for individuals in which wakefulness is critical.

39.4 Which of the following antihistamines also has mast cell–stabilizing effects and is used in the treatment of allergic conjunctivitis?

A. Chlorpheniramine
B. Desloratadine
C. Dimenhydrinate
D. Ketotifen

Correct answer = D. Ketotifen is an antihistamine with mast cell–stabilizing properties. It is available in an ophthalmic formulation which allows for targeted drug delivery in the treatment of seasonal or perennial allergic conjunctivitis. The other agents are not known to have mast cell–stabilizing properties. Chlorpheniramine and desloratadine are used in the treatment of allergic rhinitis. Dimenhydrinate (a combination of diphenhydramine and a chlorinated theophylline derivative) is used for the prevention of motion sickness.

39.5 A 55-year-old man has planned a vacation which will include a cruise. He would like to take something to help prevent motion sickness while on the cruise. Which of the following H_1-receptor blockers is most appropriate for this patient?

A. Fexofenadine
B. Loratadine
C. Meclizine
D. Cetirizine

Correct answer = C. Of the agents listed, meclizine is the most effective for prevention of motion sickness. Other options could include dimenhydrinate or

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diphenhydramine. Fexofenadine, loratadine, and cetirizine are used in the treatment of allergic rhinitis.

39.6 Which of the following drugs for migraine is matched with the appropriate mechanism of action?

A. Dihydroergotamine—5-HT_{1F} receptor agonist
B. Lasmiditan—5-$HT_{1B/1D}$ receptor agonist
C. Rizatriptan—5-$HT_{1B/1D}$ receptor antagonist
D. Ubrogepant—CGRP receptor antagonist

Correct answer = D. Ubrogepant is a CGRP antagonist. Lasmiditan (not dihydroergotamine) is a specific 5-HT_{1F} receptor agonist. Triptans such as rizatriptan are 5-$HT_{1B/1D}$ receptor agonists (not antagonists).

39.7 A 32-year-old woman is newly diagnosed with migraine headaches. She does not get relief of her headaches with ibuprofen. Which of the following is the most appropriate treatment for this patient?

A. Ergotamine
B. Lasmiditan
C. Rimegepant
D. Sumatriptan

Correct answer = D. Triptans, such as sumatriptan, are first-line therapy for moderate or severe migraines. Ergotamine is used less often due to undesirable adverse effects (nausea and vasoconstriction). Lasmiditan and rimegepant are alternatives for patients who cannot tolerate or do not respond to triptans.

39.8 A 35-year-old woman is having several severe migraines per month. The migraines are usually relieved with one or two doses of triptan drugs. Which of the following agents is the most appropriate for prophylaxis to reduce the frequency of her migraines?

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A. Dihydroergotamine
B. Ibuprofen
C. Propranolol
D. Sumatriptan

Correct answer = C. β-Blockers such as propranolol are used for prophylaxis to reduce the frequency of migraines. The other medications are all used to treat an acute migraine headache.

39.9 A 43-year-old woman has a medical history of heart failure, diabetes, and uncontrolled hypertension, along with an extensive migraine history. Her migraine headaches are impacting her ability to perform her work as a truck driver. Which of the following medications is the most appropriate for the management of acute migraine in this patient?

A. Naratriptan
B. Ubrogepant
C. Lasmiditan
D. Ergotamine

Correct answer = B. Since this patient has an extensive cardiovascular history, including uncontrolled hypertension, options A and D are not acceptable, since they can worsen her condition. Lasmiditan is a potential option; however, the sedation associated with this agent is not appropriate due to her work as a truck driver. Ubrogepant does not cause vasoconstriction like the triptans or ergot alkaloids, so it can be used in patients with cardiovascular disease, and it does not cause sedation.

39.10 A patient with a severe migraine takes a dose of sumatriptan and experiences partial relief of her headache. Six hours later the headache begins to recur. Which of the following next steps is contraindicated for this patient?

A. Administer dihydroergotamine
B. Administer naproxen
C. Administer propranolol

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D. Repeat dose of sumatriptan

Correct answer = A. Ergot alkaloids should not be administered within 24 hours of triptans, such as sumatriptan, due to the risk of coronary ischemia. Naproxen is an NSAID and is often used along with triptans to help manage the symptoms of migraine. Propranolol is a preventive agent for migraine. Administration will likely not help with the acute migraine, but it is not contraindicated. Migraine headaches commonly recur after a single dose of triptan, but in most patients, a second dose is effective in aborting the headache.

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40

Anti-Inflammatory, Antipyretic, and Analgesic Agents

Eric Dietrich, Daniel Rubin

I. OVERVIEW

Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or microbiologic agents. Inflammation is the body's effort to inactivate or destroy invading organisms, remove irritants, and set the stage for tissue repair. When healing is complete, the inflammatory process usually subsides. However, inappropriate activation of the immune system can result in inflammation and immune-mediated diseases such as rheumatoid arthritis (RA). Normally, the immune system can differentiate between self and nonself. In RA, white blood cells (WBCs) view the synovium as nonself and initiate an inflammatory attack. WBC activation leads to stimulation of T lymphocytes, which recruit and activate monocytes and macrophages. These cells secrete proinflammatory cytokines, including tumor necrosis factor (TNF)-α and interleukin (IL)-1, into the synovial cavity, ultimately leading to joint destruction and other systemic abnormalities characteristic of RA. In addition to T lymphocyte activation, B lymphocytes are also involved and produce rheumatoid factor and other autoantibodies to maintain inflammation. These defensive reactions cause progressive tissue injury, resulting in joint damage and erosions, functional disability, pain, and reduced quality of life. Pharmacotherapy for RA includes anti-inflammatory and/or immunosuppressive agents that modulate/reduce the inflammatory process, with the goals of reducing inflammation and pain and halting or slowing disease progression. The agents discussed in this chapter (Figure 40.1) include nonsteroidal anti-inflammatory drugs (NSAIDs), *celecoxib*, *acetaminophen*, and disease-

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modifying antirheumatic drugs (DMARDs). Additionally, agents used for the treatment of gout are reviewed.

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NSAIDs

Aspirin BAYER, BUFFERIN, ECOTRIN
Celecoxib CELEBREX
Diclofenac FLECTOR, PENNSAID, VOLTAREN
Diflunisal GENERIC ONLY
Etodolac GENERIC ONLY
Fenoprofen NALFON
Flurbiprofen GENERIC ONLY
Ibuprofen ADVIL, MOTRIN
Indomethacin INDOCIN
Ketorolac ACULAR, ACUVAIL
Ketoprofen GENERIC ONLY
Meclofenamate GENERIC ONLY
Mefenamic acid PONSTEL
Meloxicam MOBIC
Methyl salicylate WINTERGREEN OIL
Nabumetone GENERIC ONLY
Naproxen ALEVE, ANAPROX, NAPROSYN
Oxaprozin DAYPRO
Piroxicam FELDENE
Salsalate GENERIC ONLY
Sulindac GENERIC ONLY
Tolmetin GENERIC ONLY

Other analgesics

Acetaminophen (Paracetamol)

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~~Acetaminophen (Paracetamol)~~
OFIRMEV, TYLENOL

DRUGS FOR RHEUMATOID ARTHRITIS

Abatacept ORENCIA
Adalimumab HUMIRA
Baricitinib OLUMIANTI
Certolizumab CIMZIA
Etanercept ENBREL
Golimumab SIMPONI
Hydroxychloroquine PLAQUENIL
Infliximab INFLECTRA, REMICADE, RENFLEXIS
Leflunomide ARAVA
Methotrexate OTREXUP, TREXALL
Rituximab RITUXAN
Sarilumab KEVZARA
Sulfasalazine AZULFIDINE
Tocilizumab ACTEMRA
Tofacitinib XELJANZ
Upadacitinib RINVOQ

DRUGS FOR GOUT

Allopurinol ZYLOPRIM
Colchicine COLCRYS
Febuxostat ULORIC
Pegloticase KRYSTEXXA
Probenecid GENERIC ONLY

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Figure 40.1 Summary of anti-inflammatory drugs.NSAIDs = nonsteroidal anti-inflammatory drugs.

II. PROSTAGLANDINS

NSAIDs act through inhibition of the synthesis of prostaglandins. Thus, an understanding of NSAIDs requires comprehension of the actions and biosynthesis of prostaglandins—unsaturated fatty acid derivatives containing 20 carbons that include a cyclic ring structure. [Note: These compounds are sometimes referred to as eicosanoids; "eicosa" refers to the 20 carbon atoms.]

A. Role of prostaglandins as local mediators

Prostaglandins and related compounds are produced in minute quantities by virtually all tissues. They generally act locally on the tissues in which they are synthesized and are rapidly metabolized to inactive products at their sites of action. Therefore, prostaglandins do not circulate in the blood in significant concentrations. Thromboxanes and leukotrienes are related compounds that are synthesized from the same precursors as the prostaglandins.

B. Synthesis of prostaglandins

Arachidonic acid is the primary precursor of the prostaglandins and related compounds, and it is present as a component of the phospholipids of cell membranes. Free arachidonic acid is released from tissue phospholipids by the action of phospholipase A_2 via a process controlled by hormones and other stimuli. There are two major pathways in the synthesis of eicosanoids from arachidonic acid, the cyclooxygenase and the lipoxygenase pathways.

1.Cyclooxygenase pathway: Eicosanoids with ring structures (that is, prostaglandins, thromboxanes, and prostacyclin) are synthesized via the cyclooxygenase pathway. Two related isoforms of the cyclooxygenase enzymes exist. Cyclooxygenase-1 (COX-1) is responsible for the physiologic production of prostanoids, whereas cyclooxygenase-2 (COX-2) causes the

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elevated production of prostanoids that occurs in sites of chronic disease and inflammation. COX-1 is a constitutive enzyme that regulates normal cellular processes, such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and reproductive and kidney functions. COX-2 is constitutively expressed in tissues such as the brain, kidney, and bone. Expression at other sites can be increased during states of chronic inflammation. Differences in binding site shape have permitted the development of selective COX-2 inhibitors (Figure 40.2). Additionally, expression of COX-2 is induced by inflammatory mediators like TNF-α and IL-1 but can also be pharmacologically inhibited by glucocorticoids (Figure 40.3), which may contribute to the significant anti-inflammatory effects of these drugs.

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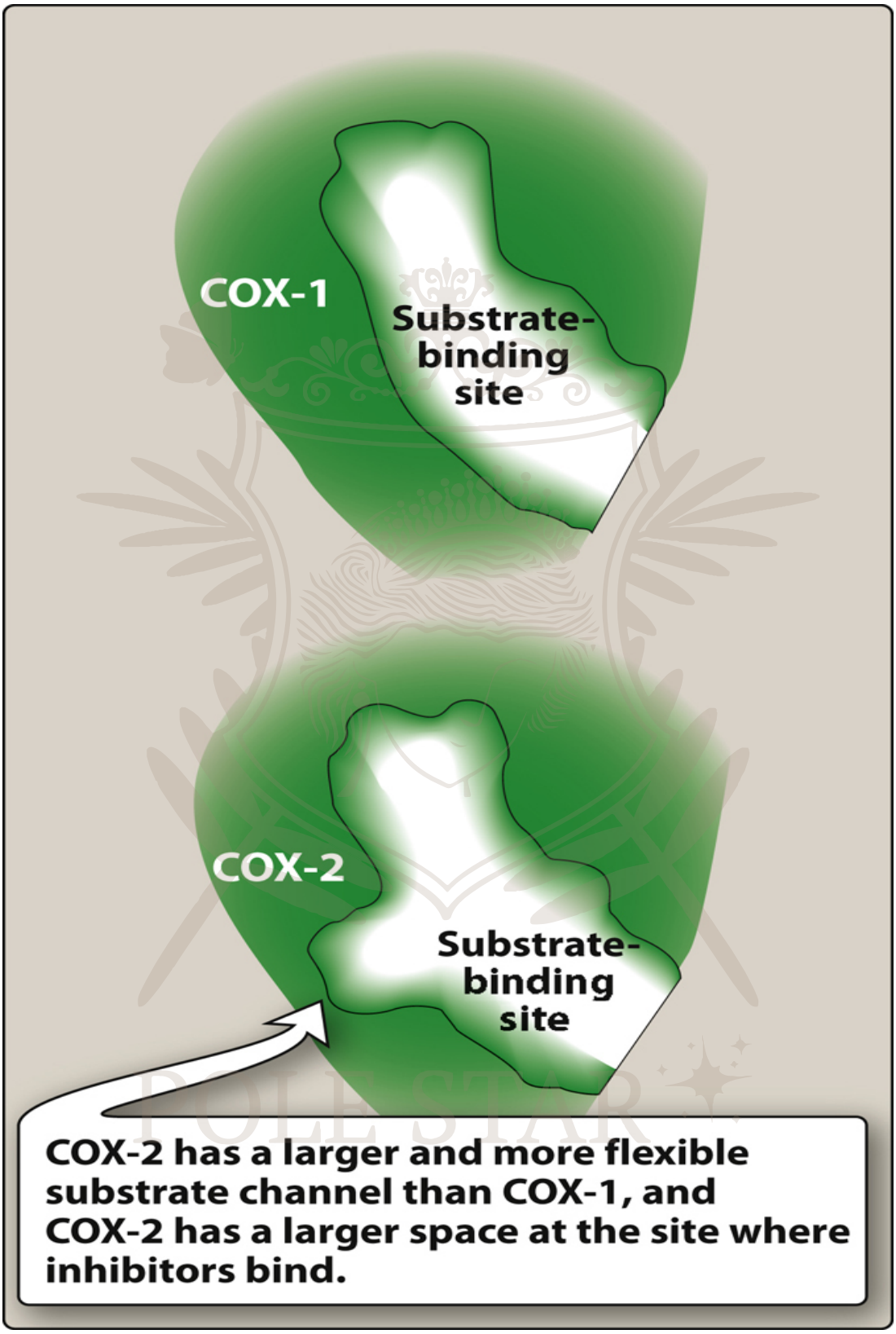
COX-1
Substrate-binding site
COX-2
Substrate-binding site
COX-2 has a larger and more flexible substrate channel than COX-1, and COX-2 has a larger space at the site where inhibitors bind.

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Figure 40.2 Structural differences in active sites of cyclooxygenase (COX)-1 and COX-2.

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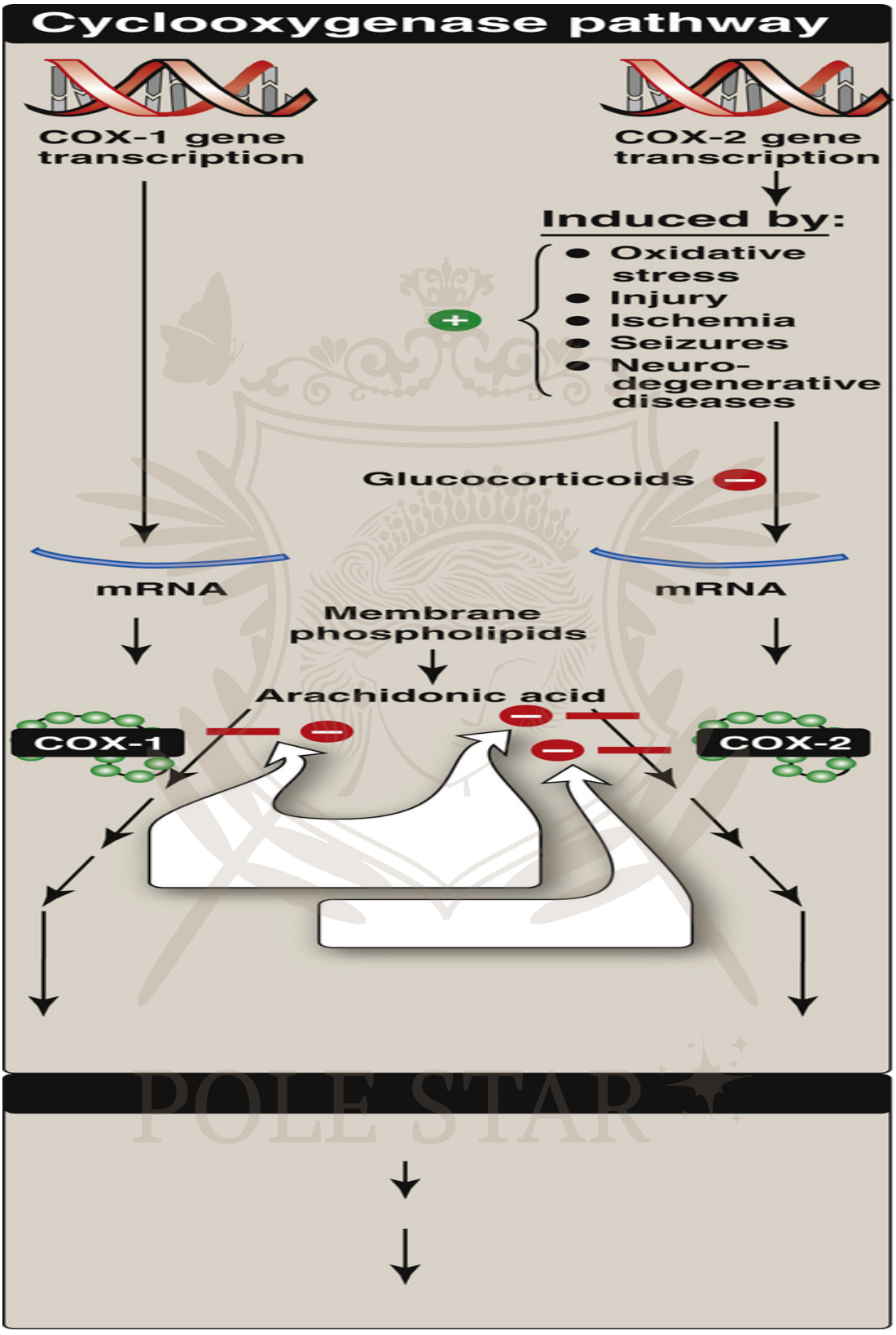

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Figure 40.3 Synthesis of prostaglandins and leukotrienes.COX = cyclooxygenase.

2.Lipoxygenase pathway: Alternatively, several lipoxygenases can act on arachidonic acid to form leukotrienes (Figure 40.3). Antileukotriene drugs, such as *zileuton*, *zafirlukast*, and *montelukast*, are treatment options for asthma (see Chapter 41).

C. Actions of prostaglandins

Actions of prostaglandins are mediated by their binding to a variety of distinct G-coupled protein receptors in cell membranes. Prostaglandins and their metabolites act as local signals that fine-tune the response of a specific cell type. Their functions vary depending on the tissue and the specific enzymes within the pathway that are available at that particular site. For example, the release of thromboxane A_2 (TXA_2) from platelets during tissue injury triggers the recruitment of new platelets for aggregation and local vasoconstriction. However, prostacyclin (PGI_2), produced by endothelial cells, has opposite effects, inhibiting platelet aggregation and producing vasodilation. The net effect on platelets and blood vessels depends on the balance of these two prostanoids.

D. Therapeutic uses of prostaglandins

Prostaglandins have a major role in modulating pain, inflammation, and fever. They control many physiological functions, such as acid secretion and mucus production in the gastrointestinal (GI) tract, uterine contractions, and renal blood flow. Prostaglandins are among the chemical mediators released in allergic and inflammatory processes. Therefore, they find use for the disorders discussed below (Figure 40.4).

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Figure 40.4 Summary of prostaglandin and prostacyclin analogs.

E. Alprostadil

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Alprostadil [al-PROS-ta-dil] is a PGE_1 analog that is naturally produced in tissues such as seminal vesicles and cavernous tissues, in the placenta, and in the ductus arteriosus of the fetus. PGE_1 maintains the patency of the ductus arteriosus during pregnancy. The ductus closes soon after delivery to allow normal blood circulation between the lungs and the heart. In neonates with congenital heart conditions, infusion of *alprostadil* keeps the ductus open, allowing time until surgical correction is possible. *Alprostadil* is also used for erectile dysfunction (see Chapter 43).

F. Lubiprostone

Lubiprostone [loo-bee-PROS-tone] is a PGE_1 derivative indicated for the treatment of chronic idiopathic constipation, opioid-induced constipation, and irritable bowel syndrome with constipation. It stimulates chloride channels in the luminal cells of the intestinal epithelium, thereby increasing intestinal fluid secretion (see Chapter 42). Nausea and diarrhea are the most common adverse effects of *lubiprostone* (Figure 40.5). Nausea can be decreased if taken with food.

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Figure 40.5 Some adverse reactions to *lubiprostone*.

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G. Misoprostol

Misoprostol [mye-soe-PROST-ole], a PGE_1 analog, is used to protect the mucosal lining of the stomach during chronic NSAID treatment. *Misoprostol* interacts with prostaglandin receptors on parietal cells within the stomach, reducing gastric acid secretion. Furthermore, *misoprostol* has a GI cytoprotective effect by stimulating mucus and bicarbonate production. This combination of effects decreases the incidence of NSAID-induced gastric ulcers. [Note: There is a combination product containing the NSAID *diclofenac* and *misoprostol*.] *Misoprostol* is also used off-label in obstetric settings for labor induction, since it increases uterine contractions by interacting with prostaglandin receptors in the uterus. *Misoprostol* has the potential to induce abortion. Therefore, the drug is contraindicated during pregnancy. Its use is limited by common adverse effects including diarrhea and abdominal pain.

H. Prostaglandin E_2 analogs

Dinoprostone [DYE-no-PROS-tone] is a synthetic PGE_2 analog used as a cervical ripening agent for labor induction and also as an abortifacient. It is administered vaginally as a removable insert or as a gel applied in the cervical canal. Administration of *dinoprostone* relaxes cervical smooth muscle and induces uterine contractions. Common adverse effects include fever, chills, nausea, diarrhea, and headache.

I. Prostaglandin $F_{2\alpha}$ analogs

Bimatoprost [bih-MAT-oh-prost], *latanoprost* [la-TAN-oh-prost], *tafluprost* [TAF-loo-prost], and *travoprost* [TRAV-oh-prost] are $PGF_{2\alpha}$ analogs that are indicated for the treatment of open-angle glaucoma. By binding to prostaglandin receptors, they increase uveoscleral outflow, reducing intraocular pressure. They are administered as ophthalmic solutions once a day and are as effective as *timolol* or better in reducing intraocular pressure. *Bimatoprost* increases eyelash prominence, length, and darkness and is approved for the treatment of eyelash hypotrichosis. Ocular reactions include blurred vision, iris color change (increased brown pigmentation), increased number and pigment of eyelashes, ocular irritation, and foreign body sensation.

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J. Prostacyclin (PGI_2) analogs

Epoprostenol [ee-poe-PROST-en-ol], the pharmaceutical form of naturally occurring prostacyclin, and the synthetic analogs of prostacyclin (*iloprost* [EYE-loe-prost] and *treprostinil* [tre-PROS-ti-nil]) are potent pulmonary vasodilators that are used for the treatment of pulmonary arterial hypertension. These drugs mimic the effects of prostacyclin in endothelial cells, producing a significant reduction in pulmonary arterial resistance with a subsequent increase in cardiac index and oxygen delivery. These agents have short half-lives. *Epoprostenol* and *treprostinil* are administered as a continuous intravenous infusion, and *treprostinil* can also be administered orally or via inhalation or subcutaneous infusion. Inhaled *iloprost* requires frequent dosing due to the short half-life (Figure 40.6). Dizziness, headache, flushing, and fainting are the most common adverse effects (Figure 40.7). Bronchospasm and cough can also occur after inhalation of *iloprost*.

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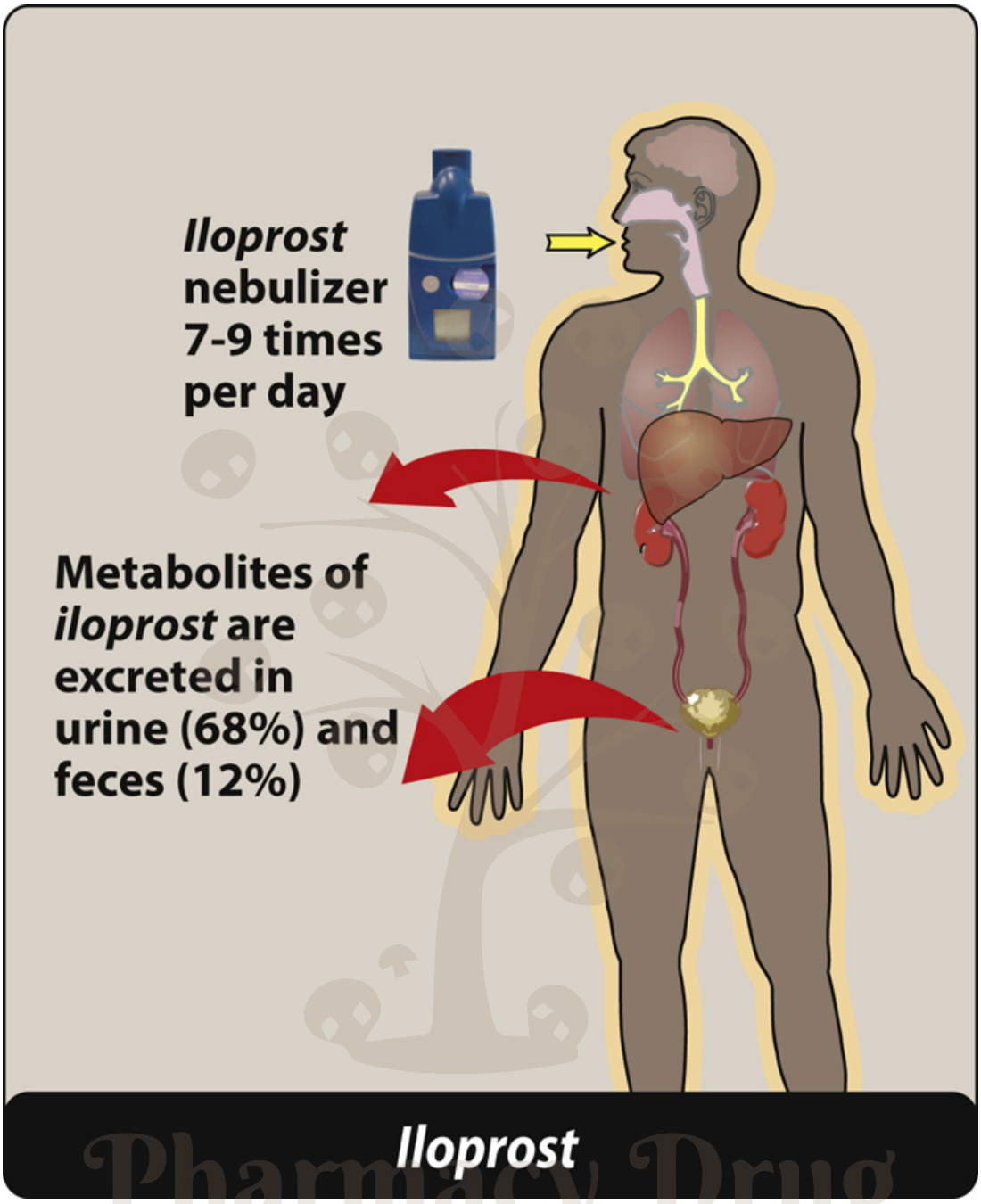

Figure 40.6 Administration and fate of *iloprost*.

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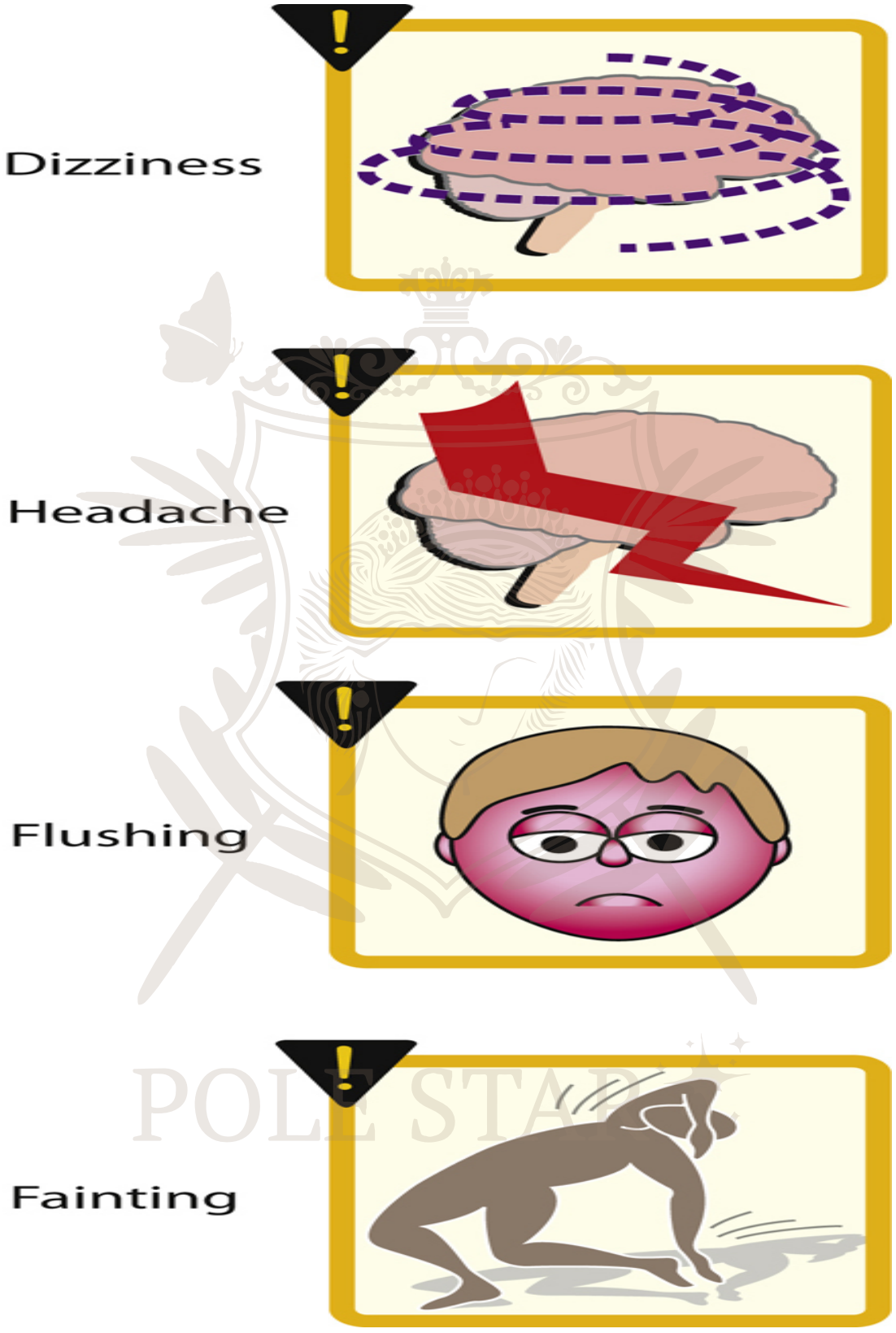

Figure 40.7 Some adverse reactions to *iloprost*.

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III. NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

NSAIDs are a group of chemically dissimilar agents that differ in their antipyretic, analgesic, and anti-inflammatory activities. The class includes derivatives of salicylic acid (*aspirin* [AS-pir-in], *diflunisal* [dye-FLOO-ni-sal], *salsalate* [SAL-sa-late]), propionic acid (*ibuprofen* [eye-bue-PROE-fen], *fenoprofen* [fen-oh-PROE-fen], *flurbiprofen* [flure-BI-proe-fen], *ketoprofen* [kee-toe-PROE-fen], *naproxen* [na-PROX-en], *oxaprozin* [ox-a-PROE-zin]), acetic acid (*diclofenac* [dye-KLOE-fen-ak], *etodolac* [ee-toe-DOE-lak], *indomethacin* [in-doe-METH-a-sin], *ketorolac* [kee-toe-ROLE-ak], *nabumetone* [na-BUE-me-tone], *sulindac* [sul-IN-dak], *tolmetin* [TOLE-met-in]), enolic acid (*meloxicam* [mel-OKS-i-kam], *piroxicam* [peer-OX-i-kam]), fenamates (*mefenamic* [me-fe-NAM-ik] *acid*, *meclofenamate* [me-kloe-fen-AM-ate]), and the selective COX-2 inhibitor (*celecoxib* [sel-e-KOX-ib]). They act primarily by inhibiting the cyclooxygenase enzymes that catalyze the first step in prostanoid biosynthesis (Figure 40.3). This leads to decreased prostaglandin synthesis with both beneficial and unwanted effects. [Note: Differences in safety and efficacy of the NSAIDs may be explained by relative selectivity for the COX-1 or COX-2 enzyme. Inhibition of COX-2 is thought to lead to the anti-inflammatory and analgesic actions of NSAIDs, whereas inhibition of COX-1 is responsible for prevention of cardiovascular events and most adverse events.]

A. Aspirin and other NSAIDs

Aspirin can be thought of as a traditional NSAID, but it exhibits anti-inflammatory activity only at relatively high doses that are rarely used. It is used more frequently at lower doses to prevent cardiovascular events such as stroke and myocardial infarction (MI). *Aspirin* is often differentiated from other NSAIDs since it is an irreversible inhibitor of cyclooxygenase activity.

1.Mechanism of action: *Aspirin* is a weak organic acid that irreversibly acetylates and, thus, inactivates cyclooxygenase

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(Figure 40.8). The other NSAIDs are reversible inhibitors of cyclooxygenase. The NSAIDs, including *aspirin*, have three major therapeutic actions: they reduce inflammation (anti-inflammatory), pain (analgesic effect), and fever (antipyretic effect; Figure 40.9). However, not all NSAIDs are equally effective in each of these actions.

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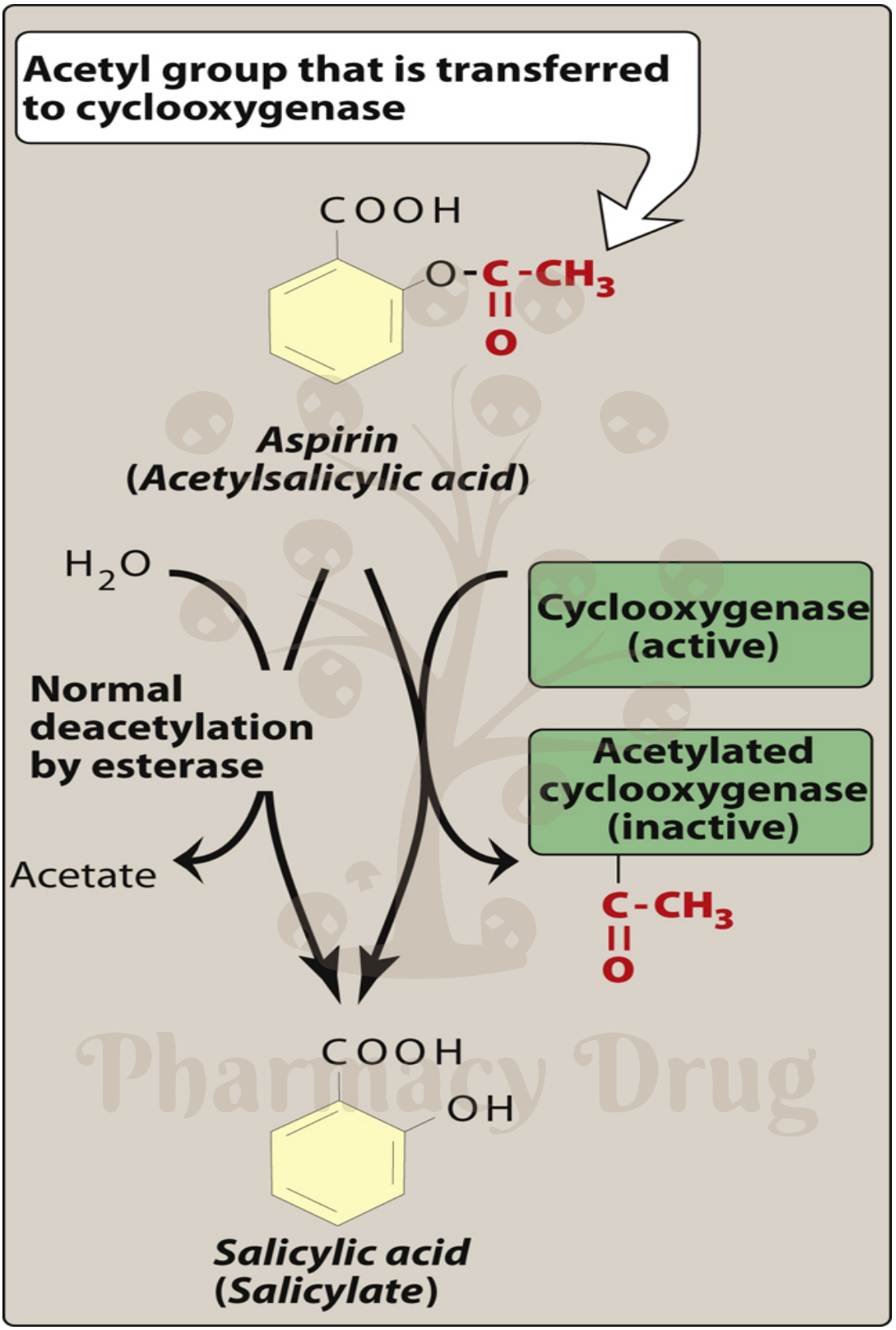

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Figure 40.8 Metabolism of aspirin and acetylation of cyclooxygenase by *aspirin*.

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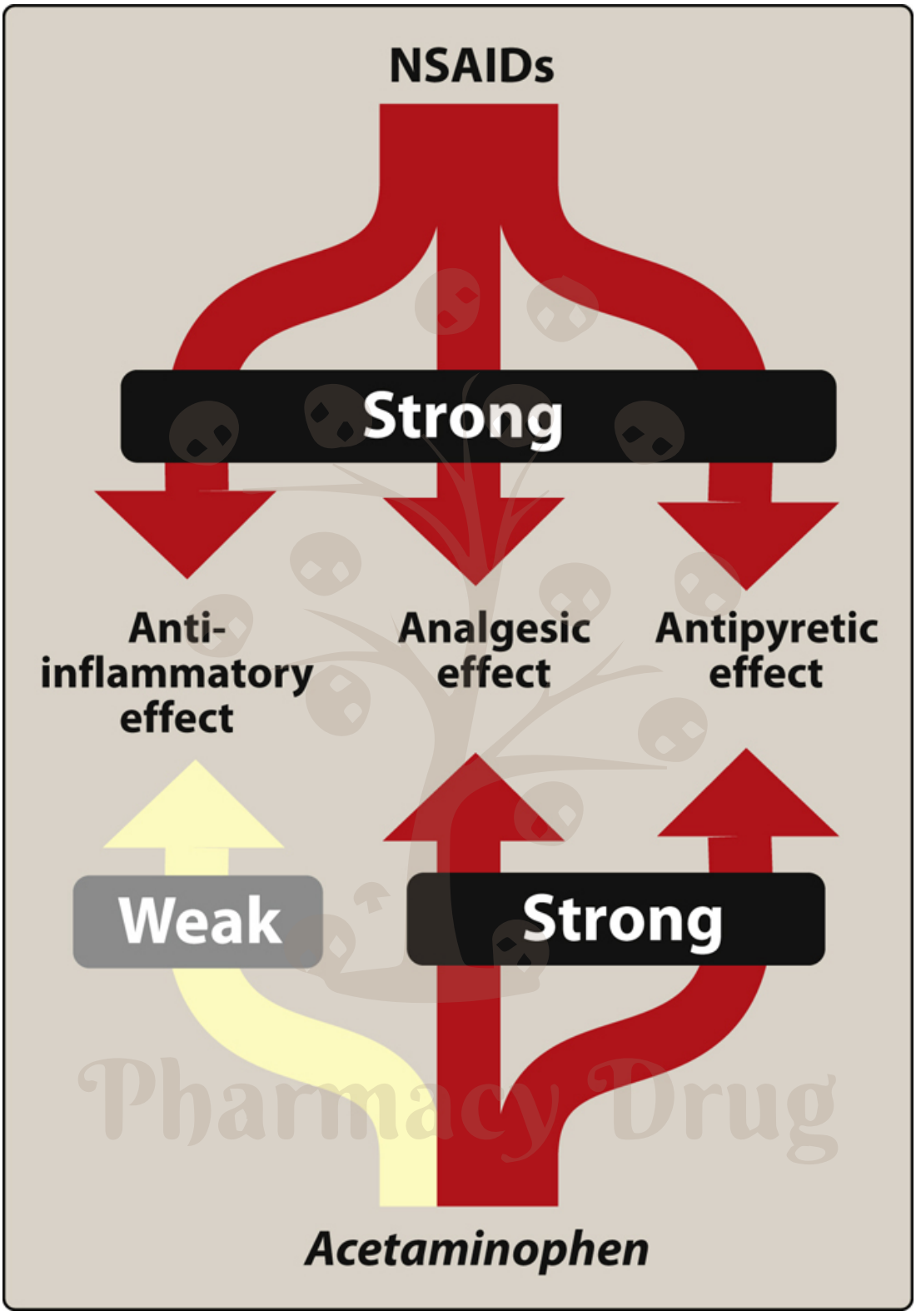

Figure 40.9 Actions of nonsteroidal anti-inflammatory drugs (NSAIDs) and *acetaminophen*.

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a. Anti-inflammatory actions: Inhibition of cyclooxygenase diminishes the formation of prostaglandins and, thus, modulates aspects of inflammation mediated by prostaglandins. NSAIDs inhibit inflammation in arthritis, but they neither arrest the progression of the disease nor induce remission.

b. Analgesic action: PGE_2 is thought to sensitize nerve endings to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process. Thus, by decreasing PGE_2 synthesis, the sensation of pain can be decreased. As COX-2 is expressed during times of inflammation and injury, it is thought that inhibition of this enzyme is responsible for the analgesic activity of NSAIDs. No single NSAID has demonstrated superior efficacy over another, and they are generally considered to have equivalent analgesic efficacy. The NSAIDs are used mainly for the management of mild to moderate pain arising from musculoskeletal disorders. One exception is *ketorolac*, which can be used for more severe pain, but for only a short duration.

c. Antipyretic action: Fever occurs when the set-point of the anterior hypothalamic thermoregulatory center is elevated. This can be caused by PGE_2 synthesis, which is stimulated when endogenous fever-producing agents (pyrogens), such as cytokines, are released from WBCs that are activated by infection, hypersensitivity, malignancy, or inflammation. The NSAIDs lower body temperature in patients with fever by impeding PGE_2 synthesis and release, resetting the "thermostat" back toward normal. This rapidly lowers the body temperature of febrile patients by increasing heat dissipation through peripheral vasodilation and sweating. NSAIDs have no effect on normal body temperature.

2.Therapeutic uses

a. Anti-inflammatory and analgesic uses: NSAIDs are used in the treatment of osteoarthritis, gout, RA, and

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common conditions requiring analgesia (for example, headache, arthralgia, myalgia, and dysmenorrhea). Combinations of opioids and NSAIDs may be effective in treating pain caused by malignancy. Furthermore, the addition of NSAIDs may lead to an opioid-sparing effect, allowing for lower doses of opioids to be utilized. The salicylates exhibit analgesic activity at lower doses. Only at higher doses do these drugs show anti-inflammatory activity (Figure 40.10). For example, two 325-mg *aspirin* tablets administered four times daily produce analgesia, whereas 12 to 20 tablets per day produce both analgesic and anti-inflammatory activity.

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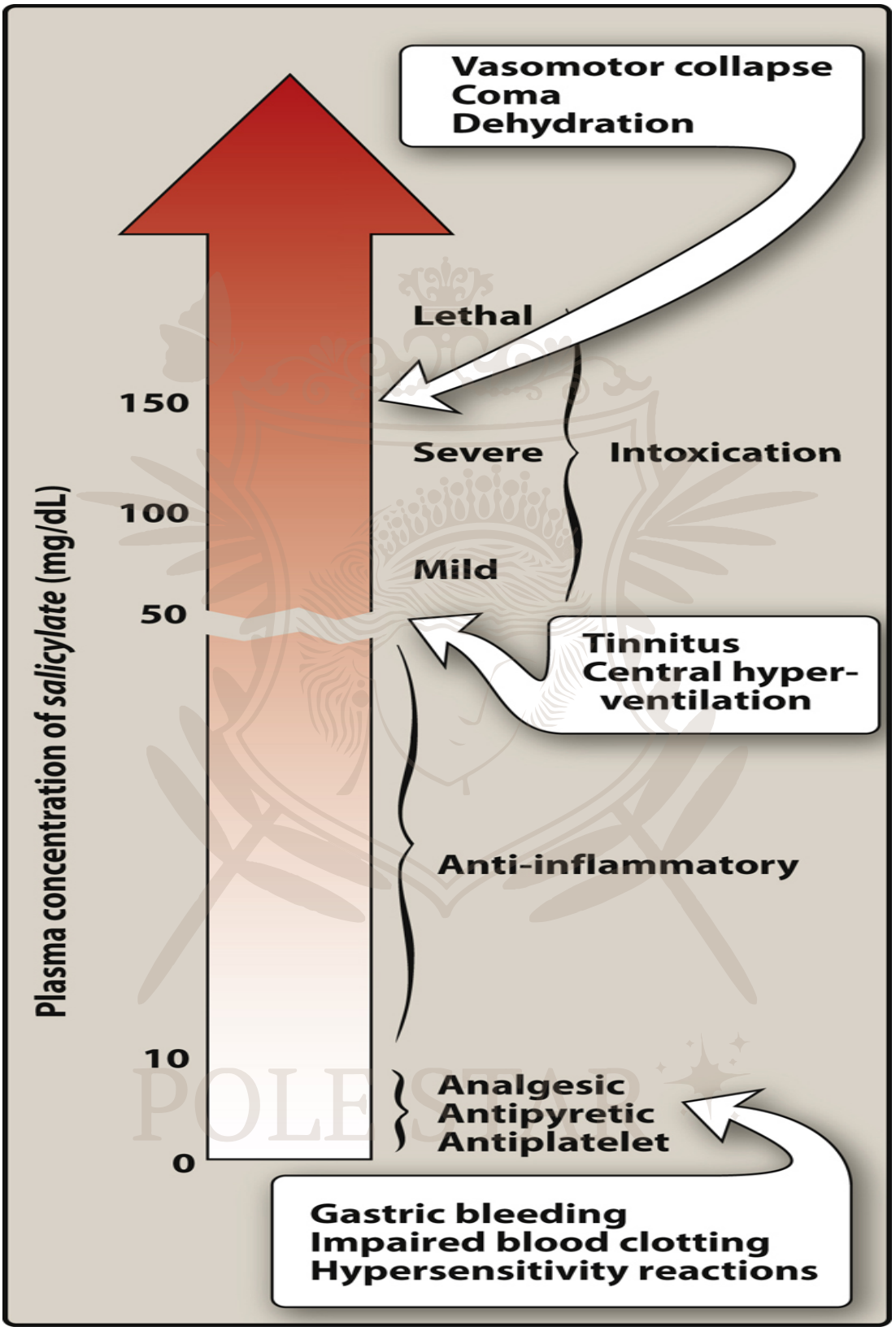

Figure 40.10 Dose-dependent effects of salicylate.

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b. Antipyretic uses: *Aspirin*, *ibuprofen*, and *naproxen* may be used to treat fever. [Note: *Aspirin* should be avoided in patients less than 19 years old with viral infections, such as varicella (chickenpox) or influenza, to prevent Reye syndrome —a syndrome that can cause fulminating hepatitis with cerebral edema, often leading to death.]

c. Cardiovascular applications: *Aspirin* irreversibly inhibits COX-1–mediated production of TXA_2, thereby reducing TXA_2-mediated vasoconstriction and platelet aggregation and the subsequent risk of cardiovascular events (Figure 40.11). The antiplatelet effects persist for the life of the platelet. Low doses of *aspirin* (75-162 mg—commonly 81 mg) are used prophylactically to reduce the risk of recurrent cardiovascular events, transient ischemic attacks (TIAs), stroke, and death in patients with a history of previous MI, TIA, or stroke. Chronic use of *aspirin* allows for continued inhibition as new platelets are generated. *Aspirin* is also used acutely to reduce the risk of death in acute MI and in patients undergoing certain revascularization procedures.

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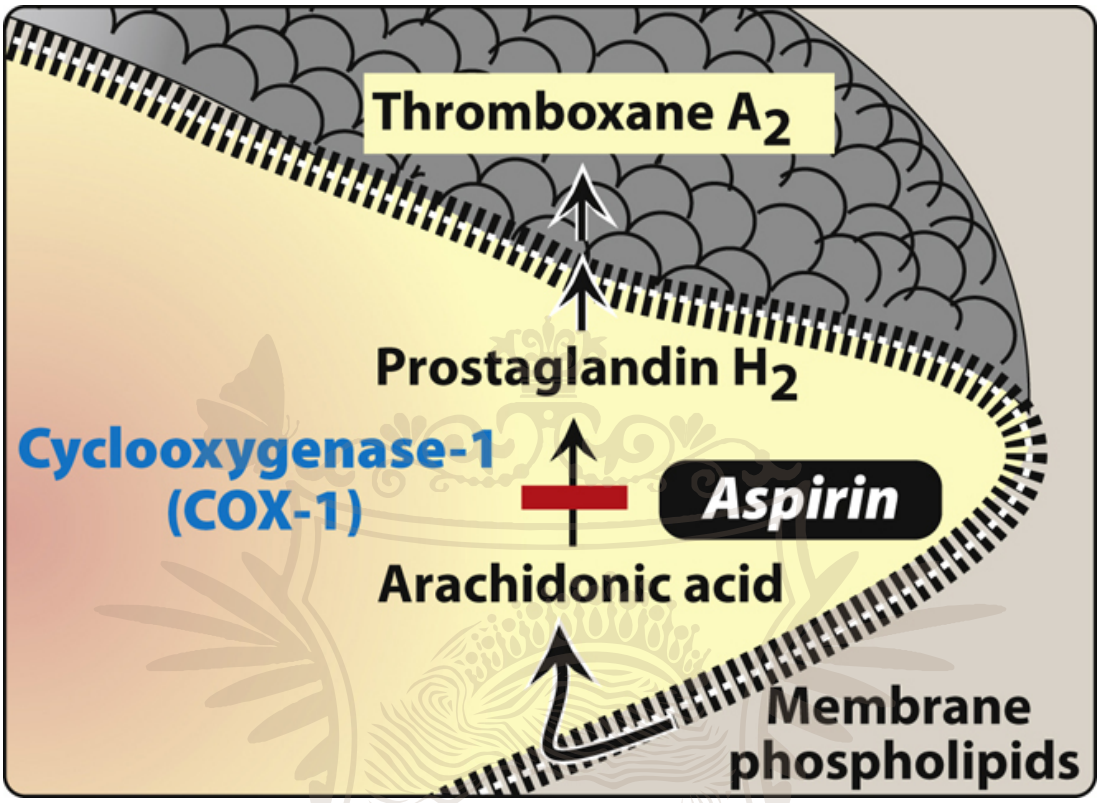

Figure 40.11 *Aspirin* irreversibly inhibits platelet cyclooxygenase-1.

d. External applications: *Salicylic acid* is used topically to treat acne, corns, calluses, and warts. *Methyl salicylate* ("oil of wintergreen") is used externally as a cutaneous counterirritant in liniments, such as arthritis creams and sports rubs. *Diclofenac* is available in topical formulations (gel or solution) for treatment of osteoarthritis in the knees or hands. In addition, ocular formulations of *ketorolac* are approved for management of seasonal allergic conjunctivitis and inflammation and pain related to ocular surgery.

3.Pharmacokinetics

a. Aspirin: After oral administration, *aspirin* is rapidly deacetylated by esterases in the body to produce salicylate. Unionized salicylates are passively absorbed mainly from the upper small intestine. Salicylates (except for *diflunisal*) cross both the blood–brain barrier and the placenta and are absorbed through intact skin (especially *methyl salicylate*). Salicylate is

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converted by the liver to water-soluble conjugates that are rapidly cleared by the kidney, resulting in first-order elimination and a serum half-life of 3.5 hours. At anti-inflammatory dosages of *aspirin* (more than 4 g/d), the hepatic metabolic pathway becomes saturated, and zero-order kinetics are observed, leading to a half-life of 12 hours or more (Figure 40.12). Salicylate is secreted into the urine and can decrease uric acid excretion at low doses. Therefore, *aspirin* should be avoided in gout, if possible, or in patients taking *probenecid*.

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Figure 40.12 Effect of dose on the half-life of *aspirin*.

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b. Other NSAIDs: Most NSAIDs are well absorbed after oral administration and circulate highly bound to plasma proteins. The majority are metabolized by the liver, mostly to inactivate metabolites. Few (for example, *nabumetone* and *sulindac*) have active metabolites. Excretion of active drug and metabolites is primarily via the urine.

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4.Adverse events: Because of the adverse-event profile, it is preferable to use NSAIDs at the lowest effective dose for the shortest duration possible.

a. Gastrointestinal: These are the most common adverse effects of NSAIDs, ranging from dyspepsia to bleeding. Normally, production of prostacyclin (PGI_2) inhibits gastric acid secretion, and PGE_2 and $PGF_{2\alpha}$ stimulate synthesis of protective mucus in both the stomach and small intestine. Agents that inhibit COX-1 reduce beneficial levels of these prostaglandins, resulting in increased gastric acid secretion, diminished mucus protection, and increased risk for GI bleeding and ulceration. Agents with a higher relative selectivity for COX-1 may have a higher risk for GI events compared with those with a lower relative selectivity for COX-1 (that is, higher COX-2 selectivity). NSAIDs should be taken with food or fluids to diminish GI upset. If NSAIDs are used in patients at high risk for GI events, proton pump inhibitors or *misoprostol* should be used concomitantly to prevent NSAID-induced ulcers (see Chapter 42).

b. Increased risk of bleeding (antiplatelet effect):: As described above, *aspirin* inhibits COX-1–mediated formation of TXA_2 and reduces platelet aggregation for the lifetime of the platelet (3-7 days). Platelet aggregation is the first step in thrombus formation, and the antiplatelet effect of *aspirin* results in a prolonged bleeding time. For this reason, *aspirin* is often withheld for at least 1 week prior to surgery to reduce the risk of bleeding. NSAIDs other than *aspirin* are not utilized for their antiplatelet effect but can still prolong bleeding time, especially when combined with anticoagulants. Concomitant use of NSAIDs and *aspirin* can prevent *aspirin* from binding to cyclooxygenase. Patients who take *aspirin* for cardioprotection should avoid concomitant NSAID use if possible or take *aspirin* at least 30 minutes prior to the NSAID.

c. Renal effects: NSAIDs prevent the synthesis of PGE_2 and PGI_2, prostaglandins that are responsible for maintaining

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renal blood flow (Figure 40.13). Decreased synthesis of prostaglandins can result in retention of sodium and water and may cause edema. Patients with a history of heart failure or kidney disease are at particularly high risk. These effects can also mitigate the beneficial effects of antihypertensive medications. In susceptible patients, NSAIDs have led to acute kidney injury.

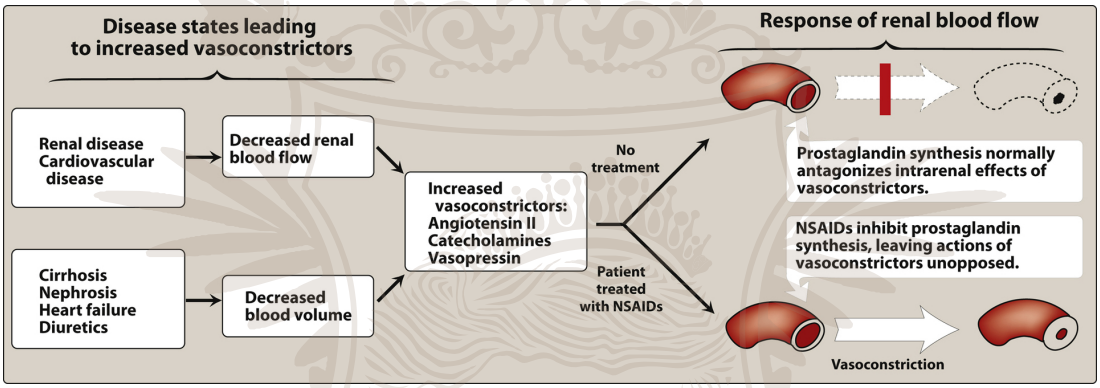

Figure 40.13 Renal effect of NSAID inhibition of prostaglandin synthesis.NSAIDs = nonsteroidal anti-inflammatory drugs.

d. Cardiac effects: Agents such as *aspirin*, with a very high degree of COX-1 selectivity at low doses, have a cardiovascular protective effect thought to be due to reduced production of TXA_2. Agents with higher relative COX-2 selectivity have been associated with an increased risk for cardiovascular events, possibly by decreasing PGI_2 production mediated by COX-2. An increased risk for cardiovascular events, including MI and stroke, has been associated with all NSAIDs except *aspirin.* All NSAIDs carry a boxed warning regarding the increased risk for cardiovascular events. Use of NSAIDs, other than *aspirin*, is discouraged in patients with established cardiovascular disease. For patients with cardiovascular disease in whom NSAID treatment cannot be avoided, *naproxen* may be the least likely to be harmful.

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e. Other adverse effects: NSAIDs are inhibitors of cyclooxygenases and, therefore, inhibit the synthesis of prostaglandins but not of leukotrienes. For this reason, NSAIDs should be used with caution in patients with asthma, as inhibition of prostaglandin synthesis can cause a shift toward leukotriene production and increase the risk of asthma exacerbations. Central nervous system (CNS) adverse events, such as headache, tinnitus, and dizziness, may occur. Approximately 15% of patients taking *aspirin* experience hypersensitivity reactions. Symptoms of true allergy include urticaria, bronchoconstriction, and angioedema. Patients with severe hypersensitivity to *aspirin* should avoid using NSAIDs.

f. Drug interactions: Salicylate is roughly 80% to 90% plasma protein bound (albumin) and can be displaced from protein-binding sites, resulting in increased concentration of free salicylate. Alternatively, *aspirin* can displace other highly protein-bound drugs, such as *warfarin*, *phenytoin*, or *valproic acid*, resulting in higher free concentrations of these agents (Figure 40.14).

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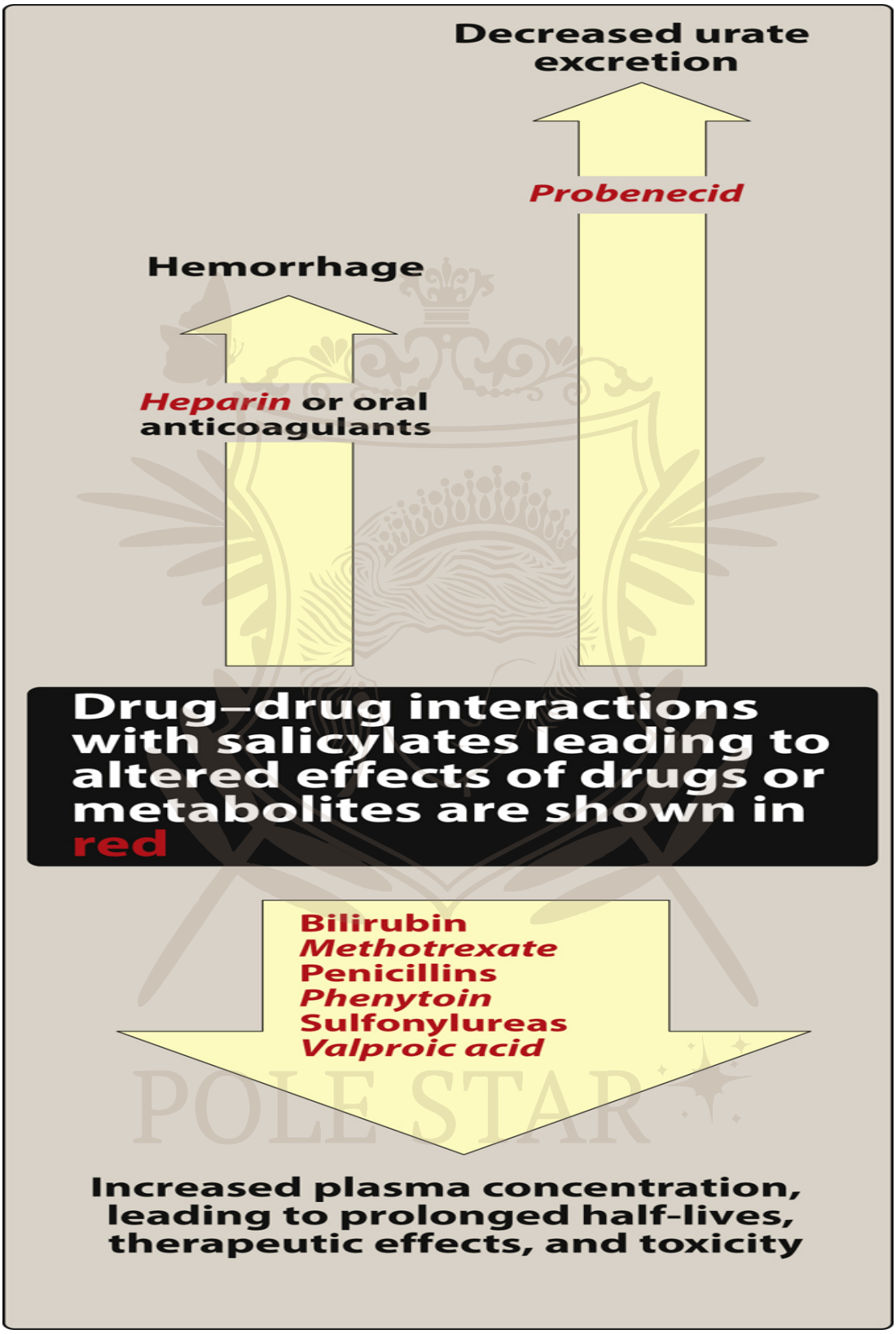

Figure 40.14 Drugs interacting with salicylates.

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g. Toxicity: Mild salicylate toxicity is called salicylism and is characterized by nausea, vomiting, marked hyperventilation, headache, mental confusion, dizziness, and tinnitus (ringing or roaring in the ears). When large doses of salicylate are administered, severe salicylate intoxication may result (see Figure 40.10). Restlessness, delirium, hallucinations, convulsions, coma, respiratory and metabolic acidosis, and death from respiratory failure may occur. Children are particularly prone to salicylate intoxication; ingestion of as little as 10 g of *aspirin* can be fatal.

h. Pregnancy: NSAIDs should be used in pregnancy only if benefits outweigh risks to the developing fetus. [Note: *Acetaminophen* is preferred if analgesic or antipyretic effects are needed during pregnancy.] In the third trimester, NSAIDs should generally be avoided due to the risk of premature closure of the ductus arteriosus.

B. Celecoxib

Celecoxib [SEL-e-KOX-ib], a selective COX-2 inhibitor, is significantly more selective for inhibition of COX-2 than COX-1 (Figure 40.15). Unlike the inhibition of COX-1 by *aspirin* (which is irreversible), the inhibition of COX-2 is reversible.

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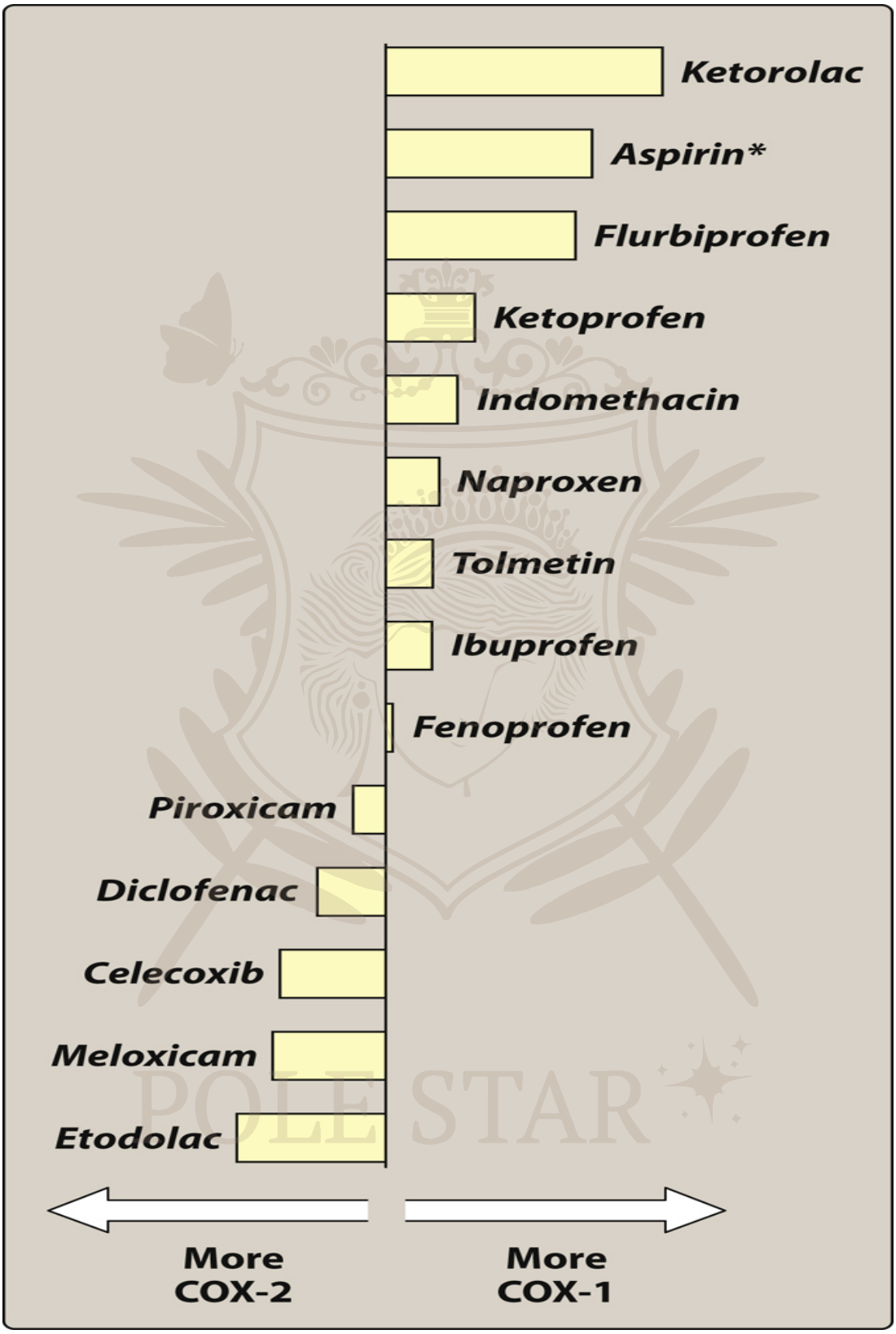

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Figure 40.15 Relative selectivity of some commonly used NSAIDs.Data shown as the logarithm of their ratio of IC_{80} (drug concentration to achieve 80% inhibition of cyclooxygenase). **Aspirin* graphed for IC_{50} value due to it showing significantly more COX-1 selectivity at lower doses and graph using higher concentrations does not accurately reflect the usage or selectivity of *aspirin*.Data from T. D.Warner , F.Giuliano , I.Vojnovic , et al. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. *Proc. Natl. Acad. Sci. U. S. A*. 96: 7563 (1999).

1.Therapeutic uses: *Celecoxib* is approved for the treatment of RA, osteoarthritis, and acute pain. *Celecoxib* has similar efficacy to NSAIDs in the treatment of pain.

2.Pharmacokinetics: *Celecoxib* is readily absorbed after oral administration. It is extensively metabolized in the liver by cytochrome P450 (CYP2C9), and the metabolites are excreted in feces and urine. The half-life is about 11 hours, and the drug may be dosed once or twice daily. The dosage should be reduced in those with moderate hepatic impairment, and *celecoxib* should be avoided in patients with severe hepatic or renal disease.

3.Adverse effects: Headache, dyspepsia, diarrhea, and abdominal pain are the most common adverse effects. *Celecoxib* is associated with less GI bleeding and dyspepsia than other NSAIDs. However, this benefit is lost when *aspirin* is added to *celecoxib* therapy. Patients who are at high risk of ulcers and require *aspirin* for cardiovascular prevention should avoid the use of *celecoxib.* Like other NSAIDs, *celecoxib* has a similar risk for cardiovascular events. Patients who have had anaphylactoid reactions to *aspirin* or nonselective NSAIDs may be at risk for similar effects with *celecoxib.* Inhibitors of CYP2C9, such as *fluconazole*, may increase serum levels of *celecoxib*.

Figure 40.16 summarizes some of the therapeutic advantages and disadvantages of members of the NSAID family.

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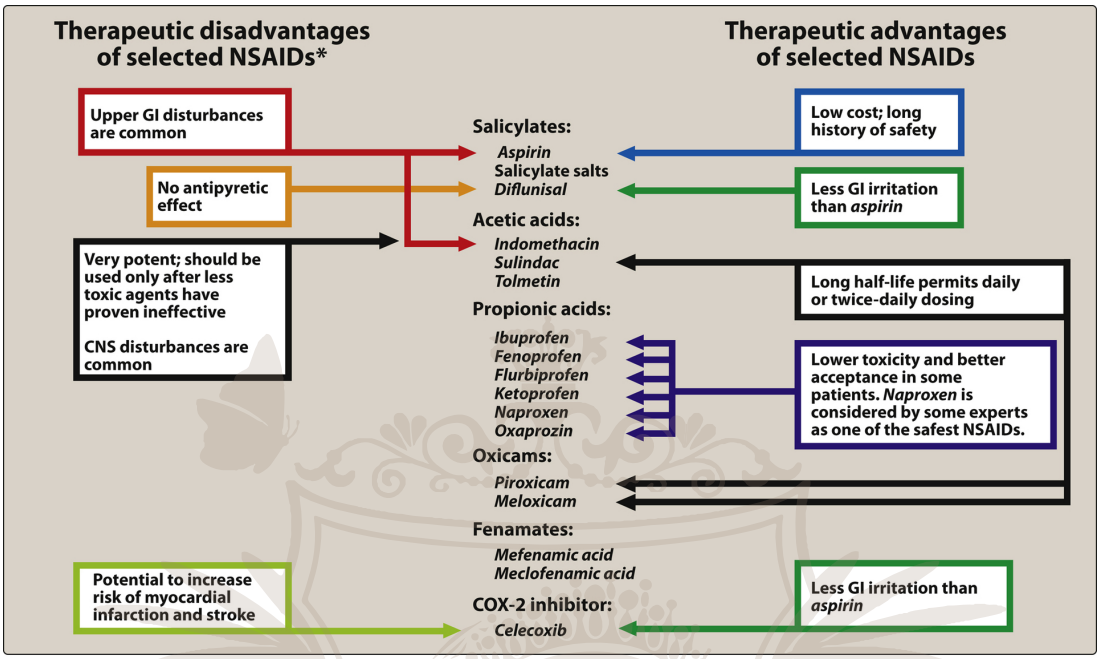

Figure 40.16 Summary of nonsteroidal anti-inflammatory agents (NSAIDs).*As a group, with the exception of *aspirin*, these drugs may have the potential to increase risk of myocardial infarction and stroke. CNS = central nervous system; COX-2 = cyclooxygenase-2; GI = gastrointestinal.

IV. ACETAMINOPHEN

Acetaminophen [a-SEET-a-MIN-oh-fen] (*N*-acetyl-*p*-aminophenol or APAP) inhibits prostaglandin synthesis in the CNS, leading to antipyretic and analgesic effects. *Acetaminophen* has less effect on cyclooxygenase in peripheral tissues (due to peripheral inactivation), which accounts for its weak anti-inflammatory activity. *Acetaminophen* does not affect platelet function or increase bleeding time. It is not considered an NSAID.

A. Therapeutic uses

Acetaminophen is used for the treatment of fever and the relief of pain. It is useful in patients with gastric complaints/risks with NSAIDs and those who do not require the anti-inflammatory action of NSAIDs. *Acetaminophen* is the analgesic/antipyretic of choice for children with viral infections or chickenpox (due to the risk of Reye syndrome with *aspirin*).

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B. Pharmacokinetics

Acetaminophen is rapidly absorbed from the GI tract and undergoes significant first-pass metabolism. It is conjugated in the liver to form inactive glucuronidated or sulfated metabolites. A portion of *acetaminophen* is hydroxylated to form *N*-acetyl-*p*-benzoquinoneimine, or NAPQI, a highly reactive metabolite that can react with sulfhydryl groups and cause liver damage. At normal doses of *acetaminophen*, NAPQI reacts with the sulfhydryl group of glutathione produced by the liver, forming a nontoxic substance (Figure 40.17). *Acetaminophen* and its metabolites are excreted in urine. The drug is also available in intravenous and rectal formulations.

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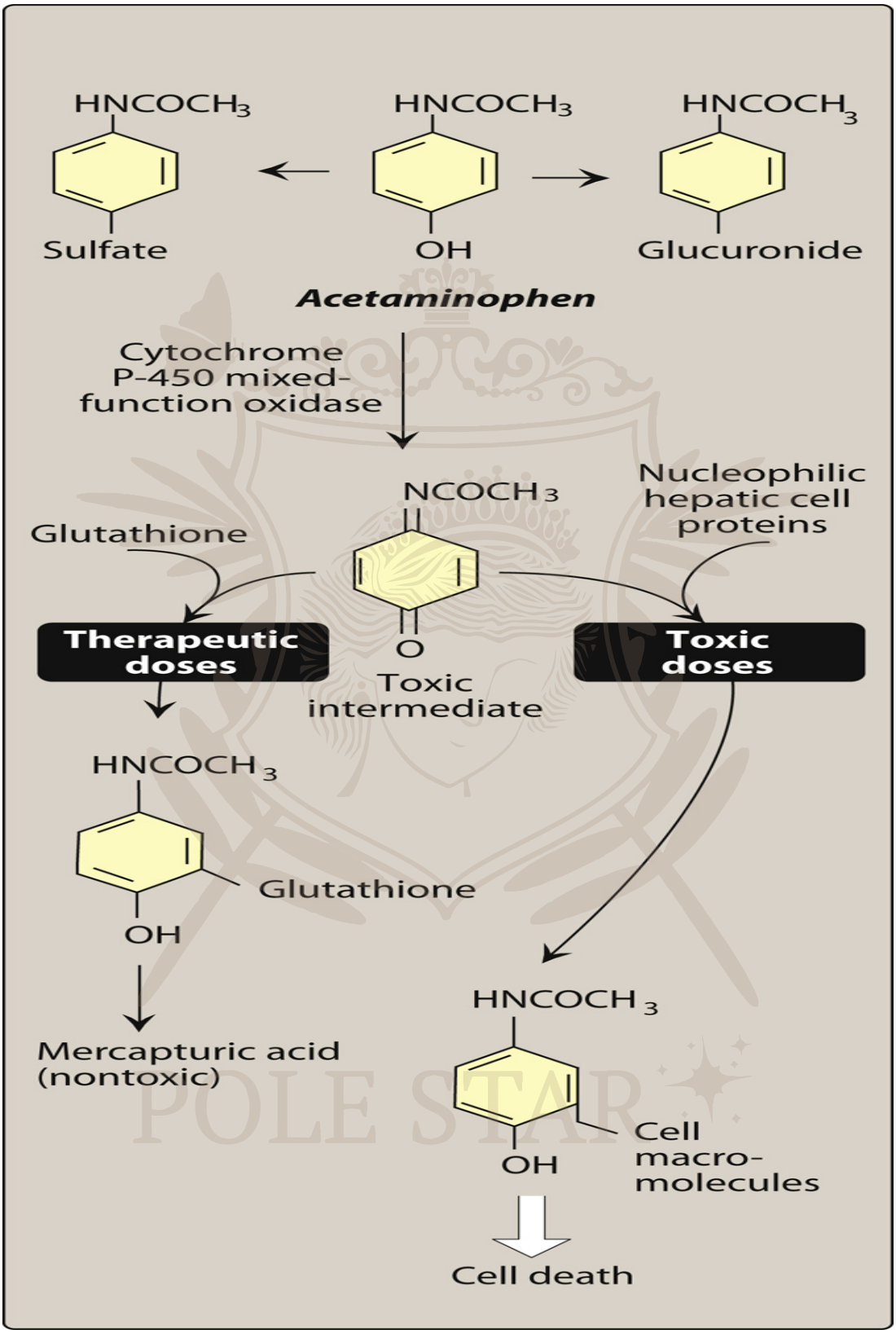

Figure 40.17 Metabolism of *acetaminophen*.

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C. Adverse effects

At normal therapeutic doses, *acetaminophen* has few significant adverse effects. With large doses of *acetaminophen*, the available glutathione in the liver becomes depleted, and NAPQI reacts with the sulfhydryl groups of hepatic proteins (see Figure 40.17). Hepatic necrosis, a serious and potentially life-threatening condition, can result. Patients with hepatic disease, viral hepatitis, chronic malnutrition, or a history of alcoholism are at higher risk of *acetaminophen*-induced hepatotoxicity. [Note: *N-acetylcysteine* is an antidote in cases of overdose (see Chapter 46).] *Acetaminophen* should be avoided in patients with severe hepatic impairment.

V. TRADITIONAL DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

Traditional DMARDs (*methotrexate*, *hydroxychloroquine*, *leflunomide*, or *sulfasalazine*) are used in the treatment of RA and have been shown to slow the course of the disease, induce remission, and prevent further destruction of the joints and involved tissues. Following diagnosis of RA, these agents should be started as soon as possible to delay progression of the disease. Monotherapy may be initiated with any of the traditional DMARDs, although *methotrexate* is generally preferred. For patients with inadequate response to monotherapy, a combination of traditional DMARDs, or addition of a biologic DMARD may be needed. NSAIDs or glucocorticoids can also be used for their anti-inflammatory actions.

A. Methotrexate

Methotrexate [meth-oh-TREX-ate] is a folic acid antagonist that inhibits cytokine production and purine nucleotide biosynthesis, leading to immunosuppressive and anti-inflammatory effects. It has become a mainstay of treatment in patients with RA. Response to *methotrexate* usually occurs within 3 to 6 weeks of starting treatment. Other traditional DMARDs or biologic DMARDs can be added to *methotrexate* if there is inadequate response to monotherapy with this agent. Doses of *methotrexate* required for RA treatment are much

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lower than those needed in cancer chemotherapy and are generally administered once weekly, thereby minimizing adverse effects. Common adverse effects of *methotrexate* when used for RA are mucosal ulceration and nausea. Cytopenias (particularly leukopenia), cirrhosis of the liver, and an acute pneumonia-like syndrome may occur with chronic administration. [Note: Supplementation with *folic acid* may improve tolerability of *methotrexate* and reduce GI and hepatic adverse effects.] Periodic liver function tests, complete blood counts, and monitoring for signs of infection are recommended. *Methotrexate* is contraindicated in pregnancy.

B. Hydroxychloroquine

Hydroxychloroquine [hye-drox-ee-KLOR-oh-kwin] is used for early, mild RA and may be combined with *methotrexate.* Its mechanism of action in autoimmune disorders is unknown, and onset of effects takes 6 weeks to 6 months. *Hydroxychloroquine* has less adverse effects on the liver and immune system than other DMARDs. However, it may cause ocular toxicity, including irreversible retinal damage and corneal deposits, CNS disturbances, GI upset, and skin discoloration and eruptions.

C. Leflunomide

Leflunomide [le-FLOO-no-mide] is an immunomodulatory agent that preferentially causes cell arrest of the autoimmune lymphocytes through its action on dihydroorotate dehydrogenase (DHODH). After biotransformation, *leflunomide* becomes a reversible inhibitor of DHODH, an enzyme necessary for pyrimidine synthesis (Figure 40.18). *Leflunomide* may be used as monotherapy in patients who have intolerance or contraindications to use of *methotrexate* in RA, or it may be used in combination with *methotrexate* for patients with suboptimal response to methotrexate alone. Common adverse effects include headache, diarrhea, and nausea. Other effects are weight loss; allergic reactions, including a flu-like syndrome; skin rash; alopecia; and hypokalemia. The drug is not recommended in patients with liver disease as it can be hepatotoxic. *Leflunomide* is contraindicated in pregnancy. Monitoring parameters include signs of infection, complete blood count, electrolytes, and liver enzymes.

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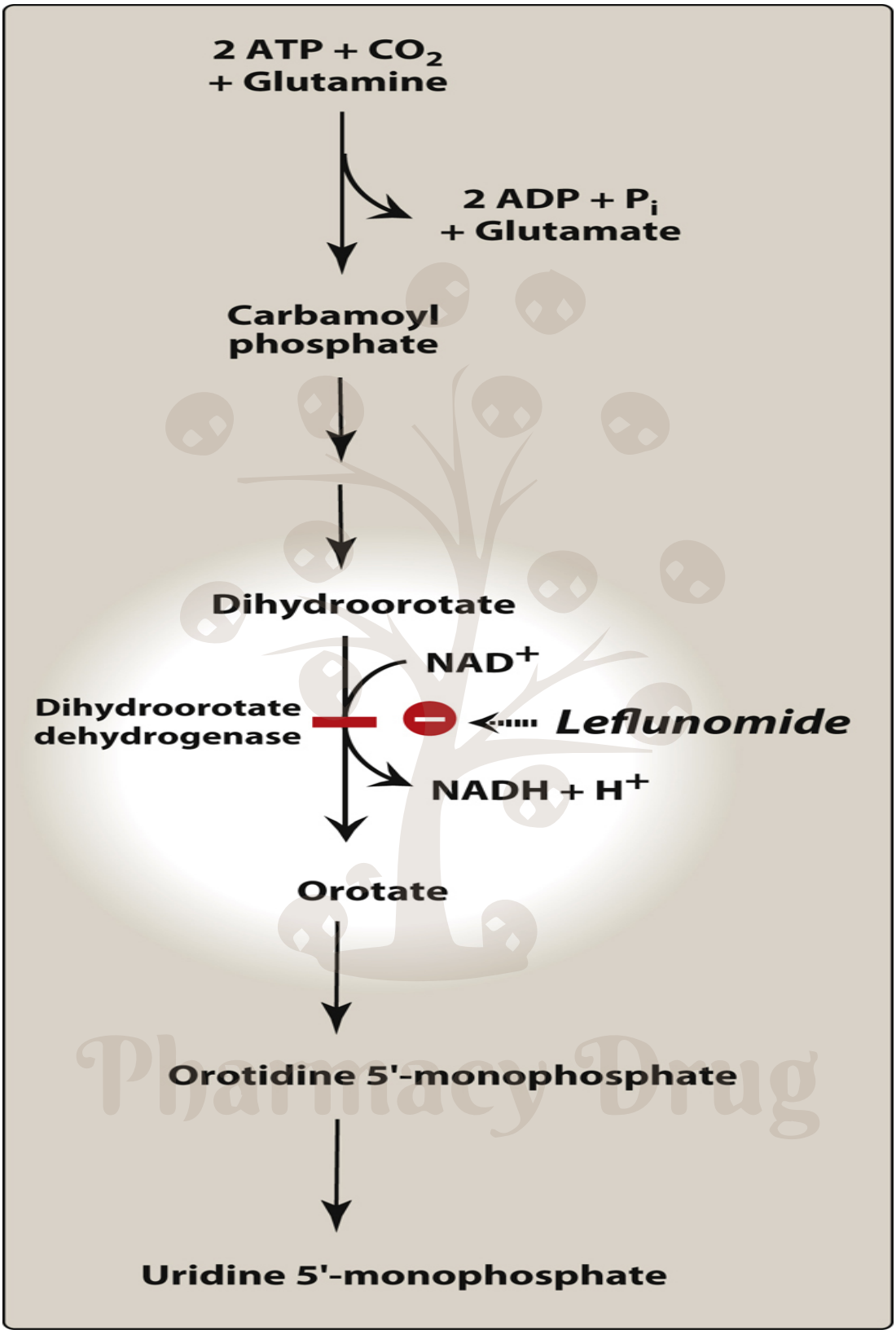

Figure 40.18 Site of action of *leflunomide*.

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D. Sulfasalazine

Sulfasalazine [sul-fa-SAH-la-zeen] has recommendations for use similar to *leflunomide* in the treatment of RA. Its mechanism of action in treating RA is unclear. The onset of activity is 1 to 3 months, and it is associated with GI adverse effects (nausea, vomiting, anorexia) and leukopenia.

E. Glucocorticoids

Glucocorticoids (see Chapter 26) are potent anti-inflammatory drugs that are commonly used in patients with RA to provide symptomatic relief and bridge the time until other DMARDs become effective. Glucocorticoids should always be used at the lowest dose and for the shortest duration possible to avoid adverse effects associated with long-term use.

Clinical Application 40.1: Diagnosis of Rheumatoid Arthritis

Early diagnosis of rheumatoid arthritis is important as the disease can lead to joint destruction and loss of function. The diagnosis is made through a combination of the clinical history, physical examination, and laboratory evaluation. Typically, inflammatory arthritis involves three or more joints, the most common being the proximal interphalangeal and metacarpophalangeal joints of the hands, wrists, and metatarsophalangeal joints of the feet, although others can be involved. Testing for positive rheumatoid factor and/or anti-citrullinated peptide antibodies (anti-CCP) and markers of inflammation such as elevated C-reactive protein or erythrocyte sedimentation rate is important. Diseases with similar clinical features must be excluded, such as psoriatic arthritis and systemic lupus erythematosus. Symptoms must be present for more than 6 weeks. Early treatment can lead to limiting or prevention of disability.

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VI. BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

IL-1 and TNF-α are proinflammatory cytokines involved in the pathogenesis of RA. When secreted by synovial macrophages, IL-1 and TNF-α stimulate synovial cells to proliferate and synthesize collagenase,

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thereby degrading cartilage, stimulating bone resorption, and inhibiting proteoglycan synthesis. The biologic DMARDs include the TNF-α inhibitors (*adalimumab*, *certolizumab*, *etanercept*, *golimumab*, and *infliximab*), the IL-6 receptor antagonists (*sarilumab*, *tocilizumab)*, the costimulation blocker *abatacept*, and the anti-CD20 antibody *rituximab.* The biologic DMARDs have been shown to decrease signs and symptoms of RA, reduce progression of structural damage, and improve physical function. Clinical response can be seen with as little as 2 weeks of therapy. The biologic DMARDs are usually employed in RA after a patient has an inadequate response to traditional DMARDs. Guidelines recommend the addition of a TNF-α inhibitor or a non-TNF biologic DMARD in patients who have had inadequate response to *methotrexate.* Patients receiving biologic DMARDs are at increased risk for infections, such as tuberculosis, fungal opportunistic infections, and sepsis. [Note: TNF-α inhibitors and non-TNF biologic DMARDs should not be used together due to the risk of severe infections.] Reactivation of hepatitis B may occur with the use of these agents. Live vaccinations should not be administered to patients taking any of the biologic DMARDs. TNF-α inhibitors should be used cautiously in those with heart failure, as they can cause and/or worsen preexisting heart failure. An increased risk of lymphoma and other cancers has been observed with the use of TNF-α inhibitors. [Note: TNF-α inhibitors find use in a number of disorders, such as ulcerative colitis and Crohn disease (see Chapter 42), psoriasis, and ankylosing spondylitis.] Characteristics of the biologic DMARDs for the treatment of RA are outlined below.

A. Adalimumab

Adalimumab [AY-da-LIM-ue-mab] is a recombinant monoclonal antibody that binds to TNF-α and interferes with its activity by blocking interaction of TNF-α with cell surface receptors. *Adalimumab* is administered subcutaneously weekly or every other week. It may cause headache, nausea, agranulocytosis, rash, reaction at the injection site, and increased risk of infections.

B. Certolizumab

Certolizumab [ser-toe-LIZ-oo-mab] is a humanized antibody that neutralizes biological actions of TNF-α. It is combined with polyethylene glycol (pegylated) and is administered every 2 weeks via

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subcutaneous injection. Adverse effects are similar to other TNF-α inhibitors.

C. Etanercept

Etanercept [ee-TAN-er-cept] is a genetically engineered fusion protein that binds to TNF-α, thereby blocking its interaction with cell surface TNF-α receptors. The combination of *etanercept* and *methotrexate* is more effective than *methotrexate* or *etanercept* alone in hindering the RA disease process, improving function and achieving remission (Figure 40.19). *Etanercept* is given subcutaneously once weekly and is generally well tolerated.

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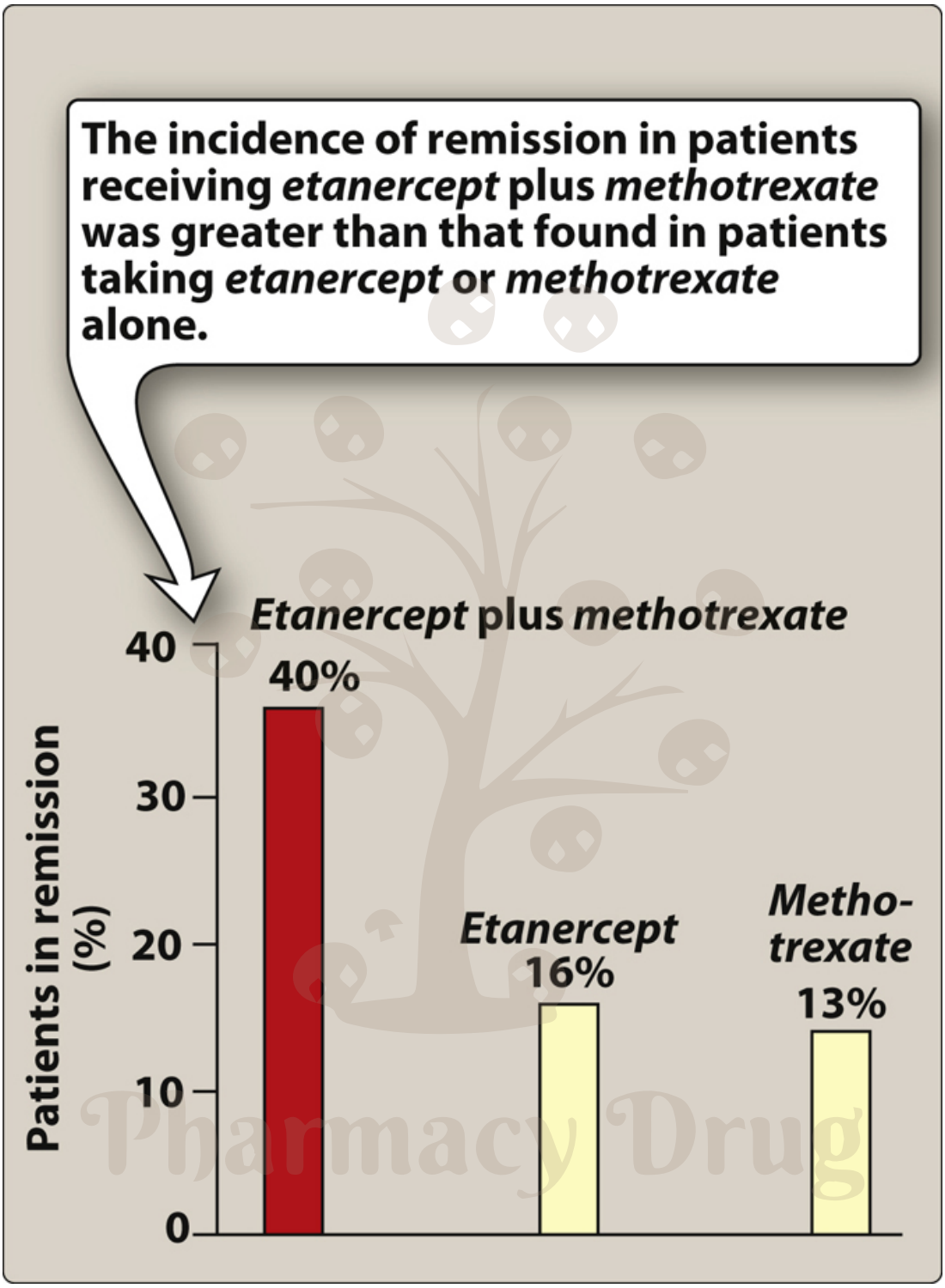

Figure 40.19 Incidence of remission from the symptoms of RA after 1 year of therapy.

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D. Golimumab

Golimumab [goe-LIM-ue-mab] neutralizes the biological activity of TNF-α by binding to it and blocking its interaction with cell surface receptors. It is administered subcutaneously once a month in combination with *methotrexate. Golimumab* may increase hepatic enzymes.

E. Infliximab

Infliximab [in-FLIX-i-mab] is a chimeric monoclonal antibody composed of human and murine regions. The antibody binds specifically to human TNF-α and inhibits binding with its receptors. This agent is not indicated for monotherapy, as this leads to the development of anti-*infliximab* antibodies and reduced efficacy. *Infliximab* should be administered with *methotrexate. Infliximab* is administered as an IV infusion every 8 weeks. Infusion-related reactions, such as fever, chills, pruritus, and urticaria, may occur.

F. Tocilizumab and sarilumab

Tocilizumab [toe-si-LIZ-ue-mab] and *sarilumab* [sar-IL-ue-mab] are recombinant monoclonal antibodies that bind to IL-6 receptors and inhibit activity of the proinflammatory cytokine IL-6. Both *tocilizumab* and *sarilumab* are administered as a subcutaneous injection every 2 weeks. *Tocilizumab* may also be administered as an intravenous infusion every 4 weeks. Adverse reactions to *tocilizumab* include elevated liver function tests, hyperlipidemia, neutropenia, hypertension, and infusion-related and injection site reactions. Adverse reactions for *sarilumab* are similar.

G. Abatacept

T lymphocytes need two interactions to become activated: (1) the antigen-presenting cell (macrophages or B cells) must interact with the receptor on the T cell and (2) the CD80/CD86 protein on the antigen-presenting cell must interact with the CD28 protein on the T cell. *Abatacept* [a-BAT-ah-cept] is a recombinant fusion protein and costimulation modulator that competes with CD28 for binding on CD80/CD86 protein, thereby preventing full T cell activation and reducing the inflammatory response. *Abatacept* is administered as an

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IV infusion every 4 weeks. Common adverse effects include infusion-related reactions, headache, upper respiratory infections, and nausea.

H. Rituximab

In RA, B lymphocytes can perpetuate the inflammatory process in the synovium by (1) activating T lymphocytes, (2) producing autoantibodies and rheumatoid factor, and (3) producing proinflammatory cytokines, such as TNF-α and IL-1. *Rituximab* [ri-TUK-si-mab] is a chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. Administration of *rituximab* results in B cell depletion. *Rituximab* is administered as an intravenous infusion every 16 to 24 weeks. To reduce infusion reactions, *methylprednisolone*, *acetaminophen*, and an antihistamine are administered prior to each infusion. Infusion reactions (urticaria, hypotension, and angioedema) are the most common complaints and typically occur during the first infusion.

VII. OTHER DRUGS FOR RHEUMATOID ARTHRITIS

Janus kinases are intracellular enzymes that modulate immune cell activity in response to the binding of inflammatory mediators to the cellular membrane. *Tofacitinib* [toe-fa-SYE-ti-nib], *baricitinib* [bar-i-SYE-ti-nib], and *upadacitinib* [ue-PAD-a-SYE-ti-nib] are synthetic small molecules that are inhibitors of Janus kinases. These oral agents are indicated for the treatment of moderate to severe established RA in patients who have had an inadequate response or intolerance to *methotrexate* and TNF-α inhibitors. Metabolism of these drugs is mediated primarily by CYP3A4, and dosage adjustments may be required if the drug is administered with potent inhibitors or inducers of this isoenzyme. Hemoglobin concentrations must be greater than 9 g/dL to start *tofacitinib* and must be monitored during therapy due to the risk for anemia. *Baracitinib* and *upadacitinib* should be avoided in patients with anemia. Likewise, lymphocyte and neutrophil counts should be checked prior to initiation of therapy and monitored during treatment with these agents. *Tofacitinib*, *baricitinib*, and *upadacitinib* may also increase

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the risk for new primary malignancy, opportunistic infections, gastrointestinal perforation, and venous thromboembolism. Due to long-term safety concerns, these agents are usually reserved for patients who have inadequate response or intolerance to other agents. Common adverse effects of the Janus kinase inhibitors include nausea and upper respiratory tract infections. [Note: *Anakinra*, *azathioprine*, *cyclosporine*, *gold*, and *minocycline* are other agents used infrequently in the treatment of RA due to their adverse effect profile or the availability of other agents with more proven efficacy.]

VIII. DRUGS USED FOR THE TREATMENT OF GOUT

Gout is a metabolic disorder characterized by high levels of uric acid in the blood (hyperuricemia). Hyperuricemia can lead to deposition of sodium urate crystals in tissues, especially the joints and kidney. The deposition of urate crystals initiates an inflammatory process involving the infiltration of granulocytes that phagocytize the urate crystals (Figure 40.20). Acute flares of gout usually present as pain, swelling, tenderness, and redness in the affected joints (for example, big toe, knees, ankles, wrists, or elbows). The cause of hyperuricemia in gout is an imbalance between overproduction of uric acid and/or the inability to excrete uric acid renally. Most therapeutic strategies for gout involve lowering the uric acid level below the saturation point (6 mg/dL), thus preventing the deposition of urate crystals. This can be accomplished by interfering with uric acid synthesis or increasing uric acid excretion.

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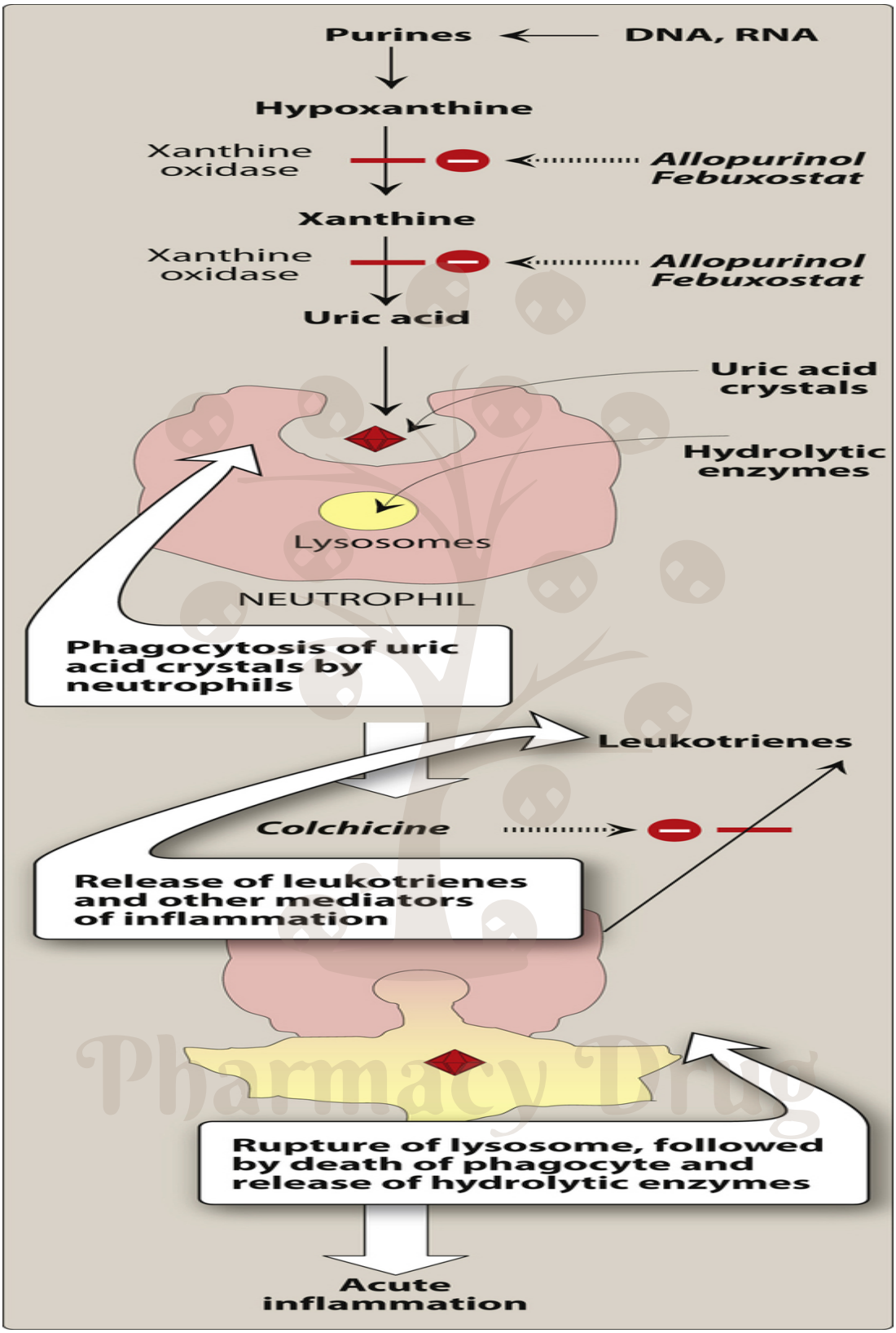

Figure 40.20 Role of uric acid in the inflammation of gout.

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A. Treatment of acute gout

Acute gout attacks can result from a number of conditions, including excessive alcohol consumption, a diet rich in purines, and kidney disease. NSAIDs, corticosteroids, and *colchicine* are effective agents for the management of acute gouty arthritis. *Indomethacin* is considered the classic NSAID of choice, although all NSAIDs are likely to be effective in decreasing pain and inflammation. Intra-articular administration of corticosteroids (when only one or two joints are affected) is also appropriate in the acute setting, or systemic corticosteroids for more widespread joint involvement. Patients are candidates for prophylactic urate-lowering therapy if they have more than two gouty attacks per year or they have chronic kidney disease, kidney stones, or tophi (deposit of urate crystals in the joints, bones, cartilage, or other body structures).

B. Treatment of chronic gout

Urate-lowering therapy for chronic gout aims to reduce the frequency of attacks and complications of gout. Treatment strategies include the use of xanthine oxidase inhibitors to reduce the synthesis of uric acid or use of uricosuric drugs to increase its excretion. Xanthine oxidase inhibitors (*allopurinol*, *febuxostat*) are first-line urate-lowering agents. Uricosuric agents (*probenecid*) may be used in patients who are intolerant to xanthine oxidase inhibitors or fail to achieve adequate response with those agents. [Note: Initiation of urate-lowering therapy can precipitate an acute gout attack due to rapid changes in serum urate concentrations. Medications for the prevention of an acute gout attack (low-dose *colchicine*, NSAIDs, or corticosteroids) can be considered upon the initiation of urate-lowering therapy and continued for at least 6 months.]

C. Colchicine

Colchicine [KOL-chi-seen], a plant alkaloid, is used for the treatment of acute gouty attacks. It is neither a uricosuric nor an analgesic agent, although it relieves pain in acute attacks of gout and at times is used chronically for the prevention of gout flares.

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1.Mechanism of action: *Colchicine* binds to tubulin, a microtubular protein, causing its depolymerization. This disrupts cellular functions, such as the mobility of neutrophils, thus decreasing their migration into the inflamed joint. Furthermore, *colchicine* blocks cell division by binding to mitotic spindles.

2.Therapeutic uses: The anti-inflammatory activity of *colchicine* is specific for gout, usually alleviating the pain of acute gout within 12 hours. [Note: *Colchicine* must be administered within 36 hours of onset of attack to be effective.] NSAIDs have largely replaced *colchicine* in the treatment of acute gouty attacks for safety reasons. *Colchicine* is also used as a prophylactic agent to prevent acute attacks of gout in patients initiating urate-lowering therapy.

3.Pharmacokinetics: *Colchicine* is administered orally and is rapidly absorbed from the GI tract. *Colchicine* is metabolized by hepatic CYP450 3A4 and other tissues. It undergoes enterohepatic recirculation and exhibits high interpatient variability in the elimination half-life. A portion of the drug is excreted unchanged in the urine.

4.Adverse effects: *Colchicine* may cause nausea, vomiting, abdominal pain, and diarrhea (Figure 40.21). Chronic administration may lead to myopathy, neutropenia, aplastic anemia, and alopecia. The drug should not be used in pregnancy and should be used with caution in patients with hepatic, renal, or cardiovascular disease. Dosage adjustments are required in patients taking CYP3A4 inhibitors (for example, *clarithromycin* and *itraconazole*) or P-gp inhibitors (for example, *amiodarone* and *verapamil*) and those with severe renal impairment.

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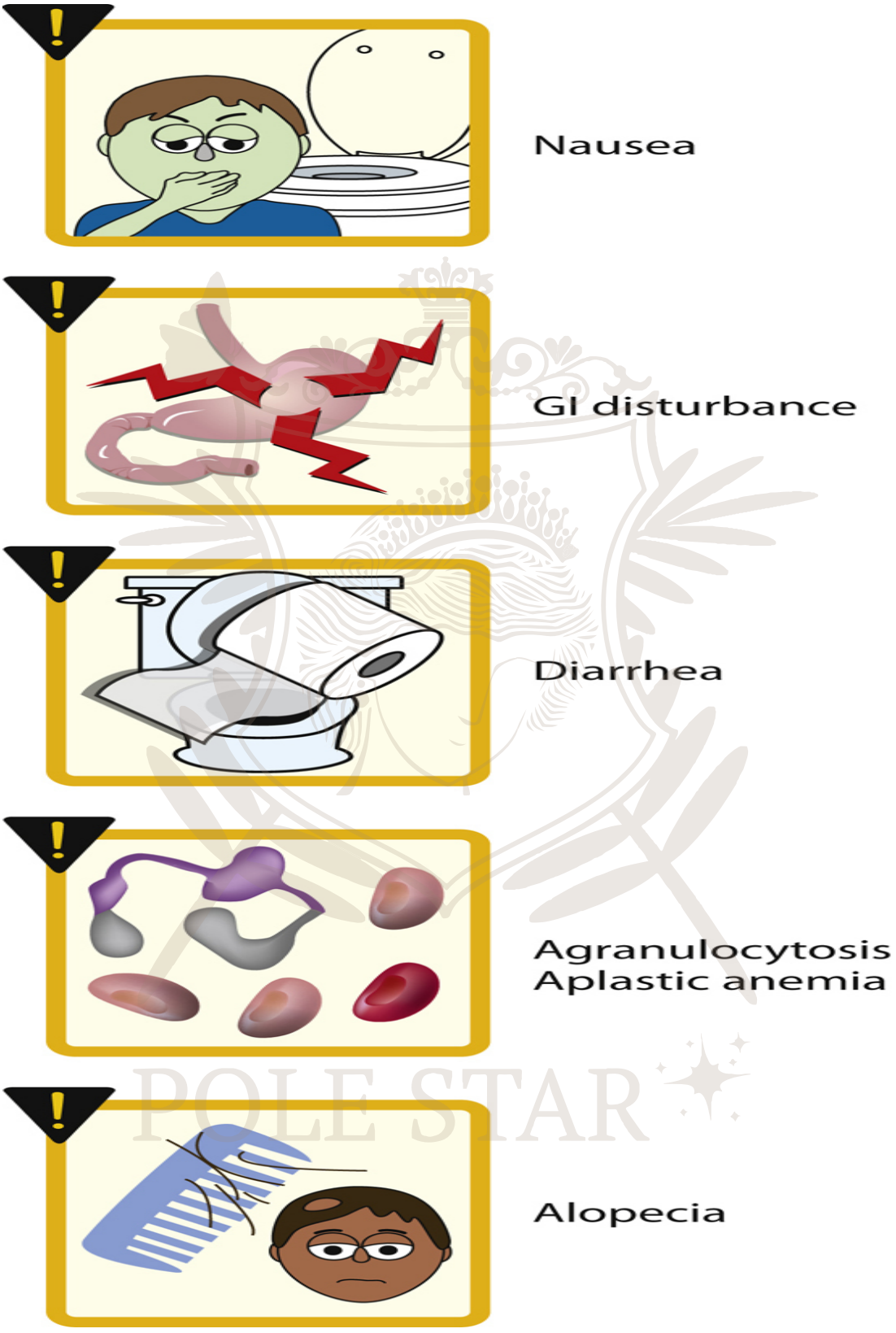

Figure 40.21 Some adverse effects of *colchicine*.GI = gastrointestinal.

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D. Allopurinol

Allopurinol [al-oh-PURE-i-nole], a xanthine oxidase inhibitor, is a purine analog. It reduces the production of uric acid by competitively inhibiting the last two steps in uric acid biosynthesis that are catalyzed by xanthine oxidase (see Figure 40.20).

1.Therapeutic uses: *Allopurinol* is an effective urate-lowering therapy in the treatment of gout and hyperuricemia secondary to other conditions, such as that associated with certain malignancies (those in which large amounts of purines are produced, particularly after chemotherapy) or in renal disease. In the management of gout, it is preferred over *febuxostat* and *probenecid* for urate-lowering therapy.

2.Pharmacokinetics: *Allopurinol* is completely absorbed after oral administration. The primary metabolite alloxanthine (oxypurinol) is also a xanthine oxidase inhibitor with a half-life of 15 to 18 hours. Thus, effective inhibition of xanthine oxidase can be maintained with once-daily dosing. The drug and its active metabolite are excreted in the urine. Dose adjustment is needed if estimated glomerular filtration rate is less than 30 mL/min/1.73 m^2.

3.Adverse effects: *Allopurinol* is well tolerated by most patients. Hypersensitivity reactions, especially skin rashes, are the most common adverse reactions. The risk is increased in those with reduced renal function. Because acute attacks of gout may occur more frequently during the first several months of therapy, *colchicine*, NSAIDs, or corticosteroids can be administered concurrently.

E. Febuxostat

Febuxostat [feb-UX-oh-stat] is an oral xanthine oxidase inhibitor structurally unrelated to *allopurinol.* Its adverse effect profile is similar to that of *allopurinol*, although the risk for rash and hypersensitivity reactions may be reduced. *Febuxostat* does not have the same degree of renal elimination as *allopurinol* and, thus, requires less adjustment in those with reduced renal function. *Febuxostat* should be

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used with caution in patients with a history of heart disease or stroke, as this agent may be associated with a greater risk of these events as compared with *allopurinol.* Due to this risk, use of *febuxostat* should be reserved for patients who have contraindications to or cannot tolerate *allopurinol*.

F. Probenecid

Probenecid [proe-BEN-a-sid] is an oral uricosuric drug. It is a weak organic acid that promotes renal clearance of uric acid by inhibiting the urate-anion exchanger in the proximal tubule. At therapeutic doses, it blocks proximal tubular reabsorption of uric acid. *Probenecid* should be avoided if the creatinine clearance is less than 50 mL/min. Adverse effects include nausea, vomiting, dermatologic reactions, and, rarely, anemia or anaphylactic reactions.

G. Pegloticase

Pegloticase [peg-LOE-ti-kase] is a recombinant form of the enzyme urate oxidase or uricase. It acts by converting uric acid to allantoin, a water-soluble nontoxic metabolite that is excreted primarily by the kidneys. *Pegloticase* is indicated for patients with gout who fail treatment with standard therapies such as xanthine oxidase inhibitors. It is administered as an IV infusion every 2 weeks. Infusion-related reactions and anaphylaxis may occur with *pegloticase*, and patients should be premedicated with antihistamines and corticosteroids.

Chapter Summary

- Prostaglandins have a major role in modulating pain, inflammation, and fever. They control many physiological functions, such as acid secretion and mucus production in the gastrointestinal (GI) tract, uterine contractions, and renal blood flow. Prostaglandin analogs find therapeutic use as gastroprotective agents (*misoprostol*), cervical ripening agents (*dinoprostone*), abortifacients (*misoprostol*, *dinoprostone*), pulmonary vasodilators for pulmonary arterial hypertension (*epoprostenol*, *iloprost*, *treprostinil*), and for the treatment of chronic constipation (*lubiprostone*) and glaucoma (*bimatoprost*, *latanoprost*, *tafluprost*, *travoprost*).
- NSAIDs are a group of chemically dissimilar agents that differ in their antipyretic, analgesic, and anti-inflammatory activities. NSAIDs act through inhibition of the cyclooxygenase (COX) enzymes, thereby reducing the synthesis of prostaglandins. These agents are used in the treatment of

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osteoarthritis, gout, RA, and common conditions requiring analgesia (headache, fever, arthralgia, myalgia, and dysmenorrhea).

- All NSAIDs can increase the risk for bleeding, renal toxicity, and cardiovascular (CV) events (except low dose *aspirin*). NSAIDs with a higher relative selectivity for COX-1 may have a higher risk for GI events, whereas agents with higher relative selectivity for COX-2 may have a higher risk for CV events.
- *Aspirin*, an irreversible inhibitor of COX, is used most frequently at lower doses to prevent cardiovascular events such as stroke and myocardial infarction.
- *Acetaminophen* inhibits prostaglandin synthesis in the CNS, leading to antipyretic and analgesic effects. *Acetaminophen* has less effects on cyclooxygenase in peripheral tissues, which accounts for its weak anti-inflammatory activity.
- At high doses (or in cases of overdose), *acetaminophen* can cause liver toxicity. Patients with hepatic disease, viral hepatitis, chronic malnutrition, or a history of alcoholism are at higher risk of *acetaminophen*-induced hepatotoxicity.
- DMARDs are used in the treatment of RA and have been shown to slow the course of the disease, induce remission, and prevent further destruction of the joints and involved tissues.
- Therapy for RA is usually initiated with a traditional DMARD, such as *methotrexate*, *hydroxychloroquine*, *leflunomide*, or *sulfasalazine. Methotrexate* is generally the preferred agent.
- The biologic DMARDs include the TNF-α inhibitors (*adalimumab*, *certolizumab*, *etanercept*, *golimumab*, and *infliximab*), the IL-6 receptor antagonists (*sarilumab*, *tocilizumab)*, the costimulation blocker *abatacept*, and the anti-CD20 antibody *rituximab.* These agents are most commonly added to RA therapy in patients who do not have an adequate response to traditional DMARDs.
- Patients receiving biologic DMARDs are at increased risk for infections, such as tuberculosis, fungal opportunistic infections, sepsis, and reactivation of hepatitis B. TNF-α inhibitors should be used cautiously in those with heart failure, as they can cause and/or worsen preexisting heart failure.
- Gout is a metabolic disorder characterized by high levels of uric acid in the blood (hyperuricemia). Deposition of sodium urate crystals in the joints can lead to acute flares of gout, which may be treated with NSAIDs (*indomethacin* or others), corticosteroids, or less frequently *colchicine.*
- Strategies to reduce the occurrence of gouty attacks include the use of xanthine oxidase inhibitors (*allopurinol*, *febuxostat*) to reduce the synthesis of uric acid or use of uricosuric drugs (*probenecid*) to increase its excretion.

STUDY QUESTIONS

Choose the ONE best answer.

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40.1 A 60-year-old man with osteoarthritis requires chronic therapy with NSAIDs. Which of the following prostaglandin agents can be added to his NSAID therapy to protect the GI mucosal lining and reduce the risk of gastric ulcers?

A. Misoprostol
B. Epoprostenol
C. Bimatoprost
D. Alprostadil

Correct answer = A. Misoprostol, a PGE_1 analog, is used for GI protection by stimulating prostaglandin receptors on parietal cells within the stomach, reducing gastric acid secretion. Furthermore, misoprostol has a GI cytoprotective effect by stimulating mucus and bicarbonate production. Epoprostenol, a PGI_2 analog, is used for the treatment of pulmonary arterial hypertension. Bimatoprost, a $PGF_{2\alpha}$ analog, is used topically in the eye for the treatment of open angle glaucoma or on the lashes for hypotrichosis. Alprostadil, a PGE_1 analog, is used to maintain patency of the ductus arteriosus in neonates with congenital heart problems; the drug can also be used for erectile dysfunction.

40.2 Which of the following statements correctly describes the proposed mechanism of cardioprotection from low-dose aspirin?

A. Aspirin preferentially inhibits COX-2 to lead to a relative reduction in thromboxane A_2 levels.
B. Aspirin preferentially inhibits COX-1 to lead to a relative reduction in thromboxane A_2 levels.
C. Aspirin preferentially inhibits COX-2 to lead to a relative reduction in prostacyclin levels.
D. Aspirin preferentially inhibits COX-1 to lead a relative reduction in prostacyclin levels.

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Correct answer = B. At low doses aspirin selectively inhibits COX-1, which reduces the production of thromboxane A_2, a substance that promotes vasoconstriction and platelet aggregation. COX-2 activity is thought to lead to relatively higher levels of prostacyclin, which causes vasodilation and inhibits platelet aggregation. Selective COX-2 inhibitors, as well as all NSAIDs, may increase the risk for CV events by inhibiting the beneficial production of prostacyclin by COX-2, thereby leading to a relative imbalance of thromboxane A_2 and promoting platelet aggregation and vasoconstriction.

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40.3 Which of the following statements is correct regarding the difference between acetaminophen and ibuprofen?

A. Acetaminophen has more anti-inflammatory effects compared with ibuprofen.
B. Acetaminophen has more renal and GI adverse effects compared with ibuprofen.
C. Acetaminophen has less risk for CV events compared with ibuprofen.
D. Acetaminophen has fewer antipyretic effects than ibuprofen.

Correct answer = C. While acetaminophen inhibits prostaglandin synthesis via COX inhibition, it is inactivated peripherally so it lacks anti-inflammatory activity and is also devoid of systemic GI, CV, and bleeding adverse effects, which are hallmarks of NSAIDs such as ibuprofen. However, as acetaminophen is active centrally, it is still able to maintain antipyretic effects similar to other NSAIDs.

40.4 A 22-year-old man presents with complaints of ankle pain and swelling from a sports injury 1 day prior. X-rays are negative for a fracture and he is directed to rest the joint and allow it to heal. Which of the following is LEAST likely to provide benefit for pain and inflammation of the swollen joint?

A. Celecoxib
B. Naproxen
C. Diclofenac
D. Acetaminophen

Correct answer = D. All NSAIDs possess analgesic and anti-inflammatory properties (making A, B, and C incorrect options). While acetaminophen inhibits the COX enzyme in the CNS and possesses analgesic and antipyretic actions, it is inactivated peripherally and, therefore, would be unlikely to alleviate inflammatory swelling associated with the joint injury.

40.5 A patient with which of the following conditions is the most appropriate candidate for use of acetaminophen to manage chronic pain associated with osteoarthritis?

A. Chronic malnutrition

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B. Obesity
C. Alcoholism
D. Viral hepatitis

Correct answer = B. All of the conditions except obesity can increase the risk of acetaminophen-related hepatotoxicity. Acetaminophen can deplete glutathione concentrations in the liver, allowing the toxic metabolite of acetaminophen, NAPQI, to build up. Conditions such as malnutrition can lead to low levels of glutathione to begin with (making A incorrect). Alcoholism can use up endogenous glutathione (making C incorrect). Viral hepatitis can damage the liver and, therefore, increase the susceptibility to additional damage from acetaminophen (making D incorrect). While obesity is not associated with improved health outcomes, obesity alone would not increase the risk for acetaminophen-induced liver toxicity.

40.6 A 64-year-old man presents with mild to moderate osteoarthritis knee pain in both knees. He states that he has tried acetaminophen without relief. His medical history includes diabetes, hypertension, hyperlipidemia, gastric ulcer (resolved), and coronary artery disease. Which of the following is the most appropriate NSAID regimen to treat his pain?

A. Celecoxib
B. Indomethacin and famotidine
C. Naproxen and pantoprazole
D. Naproxen

Correct answer = C. This patient is at high risk of future ulcers, due to the history of gastric ulcer. Therefore, using a regimen that includes an agent that is more COX-2 selective or a proton pump inhibitor (for example, pantoprazole) is warranted. Therefore, D is incorrect. Choices A and B are incorrect because this patient has significant cardiovascular risk and a history of coronary artery disease; additionally, B is incorrect as an H_2 receptor antagonist such as famotidine would likely be inadequate to protect against an NSAID-induced ulcer. Naproxen is thought of as the safest NSAID regarding cardiovascular disease, although it still can present risks. Therefore, C is correct as it uses the first-choice NSAID with the GI protection of a proton pump inhibitor.

40.7 A 64-year-old woman with RA and heart failure was started on methotrexate and has had an inadequate response. Which of the

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following agents is the most appropriate addition to her methotrexate therapy?

A. Adalimumab
B. Etanercept
C. Infliximab
D. Tocilizumab

Correct answer = D. Adalimumab, etanercept, and infliximab are TNF-α inhibitors that should be used with caution in patients with heart failure. Tocilizumab is a non-TNF biologic DMARD and is most appropriate to add, given the coexisting condition of heart failure.

40.8 Which statement correctly represents the mechanism of action of tofacitinib in the treatment of RA?

A. TNF-α inhibitor
B. Janus kinase inhibitor
C. IL-6 receptor blocker
D. Dihydrofolate reductase inhibitor

Correct answer = B. Tofacitinib is an inhibitor of Janus kinases 1, 3, and, to a lesser extent, 2. Methotrexate inhibits dihydrofolate reductase. Etanercept is an example of TNF-α inhibitor, and tocilizumab is an example of an IL-6 inhibitor.

40.9 A 62-year-old man presents with signs and symptoms of an acute gouty flare. Which of the following strategies is the most appropriate to acutely improve his gout symptoms and pain?

A. Allopurinol
B. Colchicine
C. Probenecid
D. Febuxostat

Correct answer = B. While all of the agents can be used for prevention of gout, colchicine is the only one that is used for an acute gout attack due to its anti-inflammatory properties. Probenecid is a uricosuric agent indicated to lower serum urate levels to prevent gout attacks. Allopurinol and febuxostat are xanthine oxidase inhibitors. They primarily act by decreasing uric acid production and are used for gout prevention.

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40.14 A 54-year-old man with gout is found to have overproduction of uric acid. Which of the following drugs is an oral agent used for gout prevention that targets the cause of his gout attacks?

A. Allopurinol
B. Colchicine
C. Probenecid
D. Pegloticase

Correct answer = A. Allopurinol is a xanthine oxidase inhibitor, which primarily acts by decreasing uric acid production. Probenecid is a uricosuric agent that increases renal excretion by inhibiting the urate–anion exchanger in the proximal tubule, thereby blocking reabsorption of uric acid and facilitating its excretion. Pegloticase works by increasing renal excretion of uric acid as well and is administered by IV infusion.

POLE STAR

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41

Drugs for Disorders of the Respiratory System

Aksha Memon

I. OVERVIEW

Asthma, chronic obstructive pulmonary disease (COPD), and allergic rhinitis are commonly encountered respiratory disorders. Each of these conditions may be associated with a troublesome cough, which may be the only presenting complaint. Asthma is a chronic disease characterized by hyperresponsive airways that affects over 341 million patients worldwide. This disorder is underdiagnosed and undertreated, creating a substantial burden to individuals and families and resulting in millions of emergency room visits. COPD is a group of diseases characterized by progressive, irreversible, airflow obstruction that affects over 251 million patients worldwide. COPD is currently the fourth leading cause of death in the world and is predicted to become the third leading cause of death by 2030. Allergic rhinitis is a common chronic disease that affects about 10% to 30% of the population worldwide and is characterized by itchy, watery eyes, runny nose, and a nonproductive cough that can significantly decrease quality of life. Each of these respiratory conditions may be managed with a combination of lifestyle changes and medications. Drugs used to treat respiratory conditions can be delivered topically to the nasal mucosa, inhaled into the lungs, or administered orally or parenterally for systemic absorption. Local delivery methods, such as nasal sprays or inhalers, are preferred to target affected tissues while minimizing systemic adverse effects.

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Medications used to treat common respiratory disorders are summarized in Figure 41.1.

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MEDICATION	INDICATION
SHORT-ACTING β_2 ADRENERGIC AGONISTS (SABAs)	
Albuterol PROAIR, PROVENTIL, VENTOLIN	Asthma, COPD
Levalbuterol XOPENEX	Asthma, COPD
LONG-ACTING β_2 ADRENERGIC AGONISTS (LABAs)	
Arformoterol BROVANA	COPD
Formoterol FORADIL, PERFOROMIST	Asthma, COPD
Indacaterol ARCAPTA	COPD
Olodaterol STRIVERDI RESPIMAT	COPD
Salmeterol SEREVENT	Asthma, COPD
INHALED CORTICOSTEROIDS	
Beclomethasone BECONASE AQ*, QVAR	Allergic rhinitis, Asthma, COPD
Budesonide PULMICORT, RHINOCORT*	Allergic rhinitis, Asthma, COPD
Ciclesonide ALVESCO, OMNARIS*, ZETONNA*	Allergic rhinitis, Asthma
Fluticasone FLONASE*, FLOVENT	Allergic rhinitis, Asthma, COPD
Mometasone ASMANEX, NASONEX*	Allergic rhinitis, Asthma
Triamcinolone NASACORT*	Allergic rhinitis, Asthma
LONG-ACTING β_2 ADRENERGIC AGONIST/CORTICOSTEROID COMBINATION	
Formoterol/budesonide SYMBICORT	Asthma, COPD
Formoterol/mometasone DULERA	Asthma, COPD
Salmeterol/fluticasone ADVAIR	Asthma, COPD
Vilanterol/fluticasone BREO ELLIPTA	COPD
SHORT-ACTING MUSCARINIC ANTAGONIST (SAMA)	
Ipratropium ATROVENT	Allergic rhinitis, Asthma, COPD
SHORT-ACTING β2 AGONIST/SHORT-ACTING ANTICHOLINERGIC COMBINATION	
Albuterol/ipratropium COMBIVENT RESPIMAT, DUONEB	COPD
LONG-ACTING ANTICHOLINERGIC (LAMA)	
Aclidinium TUDORZA PRESSAIR	COPD
Glycopyrrolate LONHALA MAGNAIR	COPD
Revefenacin YUPELRI	COPD
Tiotropium SPIRIVA	Asthma, COPD
Umeclidinium INCRUSE ELLIPTA	COPD
LABA/LAMA COMBINATION	
Formoterol/aclidinium DUAKLIR PRESSAIR	COPD
Formoterol/glycopyrrolate BEVESPI AEROSPHERE	COPD
Vilanterol/umeclidinium ANORO ELLIPTA	COPD
Olodaterol/tiotropium STIOLTO RESPIMAT	COPD
LEUKOTRIENE MODIFIERS	
Montelukast SINGULAIR	Asthma, Allergic rhinitis
Zafirlukast ACCOLATE	Asthma
Zileuton ZYFLO CR	Asthma
AGENTS FOR COUGH	
Benzonatate TESSALON PERLES	Cough suppressant
Codeine (with guaifenesin) VARIOUS	Cough suppressant/expectorant
Dextromethorphan VARIOUS	Cough suppressant
Dextromethorphan (with guaifenesin) VARIOUS	Cough suppressant/expectorant
Guaifenesin VARIOUS	Expectorant
OTHER AGENTS	
Benralizumab FASENRA	Asthma
Cromolyn NASALCROM*	Asthma, Allergic rhinitis
Dornase alfa PULMOZYME	Cystic fibrosis
Dupilumab DUPIXENT	Asthma
Mepolizumab NUCALA	Asthma
Omalizumab XOLAIR	Asthma
Reslizumab CINQAIR	Asthma
Roflumilast DALIRESP	COPD
Theophylline ELIXOPHYLLIN, THEO-24	Asthma, COPD

Figure 41.1 Summary of drugs affecting the respiratory system.*Indicates intranasal formulation used for allergic rhinitis. LABA = long-acting β_2 agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting β_2 agonist; SAMA = short-acting muscarinic antagonist.

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II. PREFERRED DRUGS USED TO TREAT ASTHMA

Asthma is a chronic inflammatory disease of the airways characterized by episodes of acute bronchoconstriction that cause shortness of breath, cough, chest tightness, wheezing, and rapid respiration.

A. Pathophysiology of asthma

Airflow obstruction in asthma is due to bronchoconstriction that results from contraction of bronchial smooth muscle, inflammation of the bronchial wall, and increased secretion of mucus (Figure 41.2). The underlying inflammation of the airways contributes to airway hyperresponsiveness, airflow limitation, respiratory symptoms, and disease chronicity. Asthma attacks may be triggered by exposure to allergens, exercise, stress, and respiratory infections. Unlike COPD, cystic fibrosis, and bronchiectasis, asthma is usually not a progressive disease. However, if untreated, asthma may cause airway remodeling, resulting in increased severity and incidence of asthma exacerbations and/or death.

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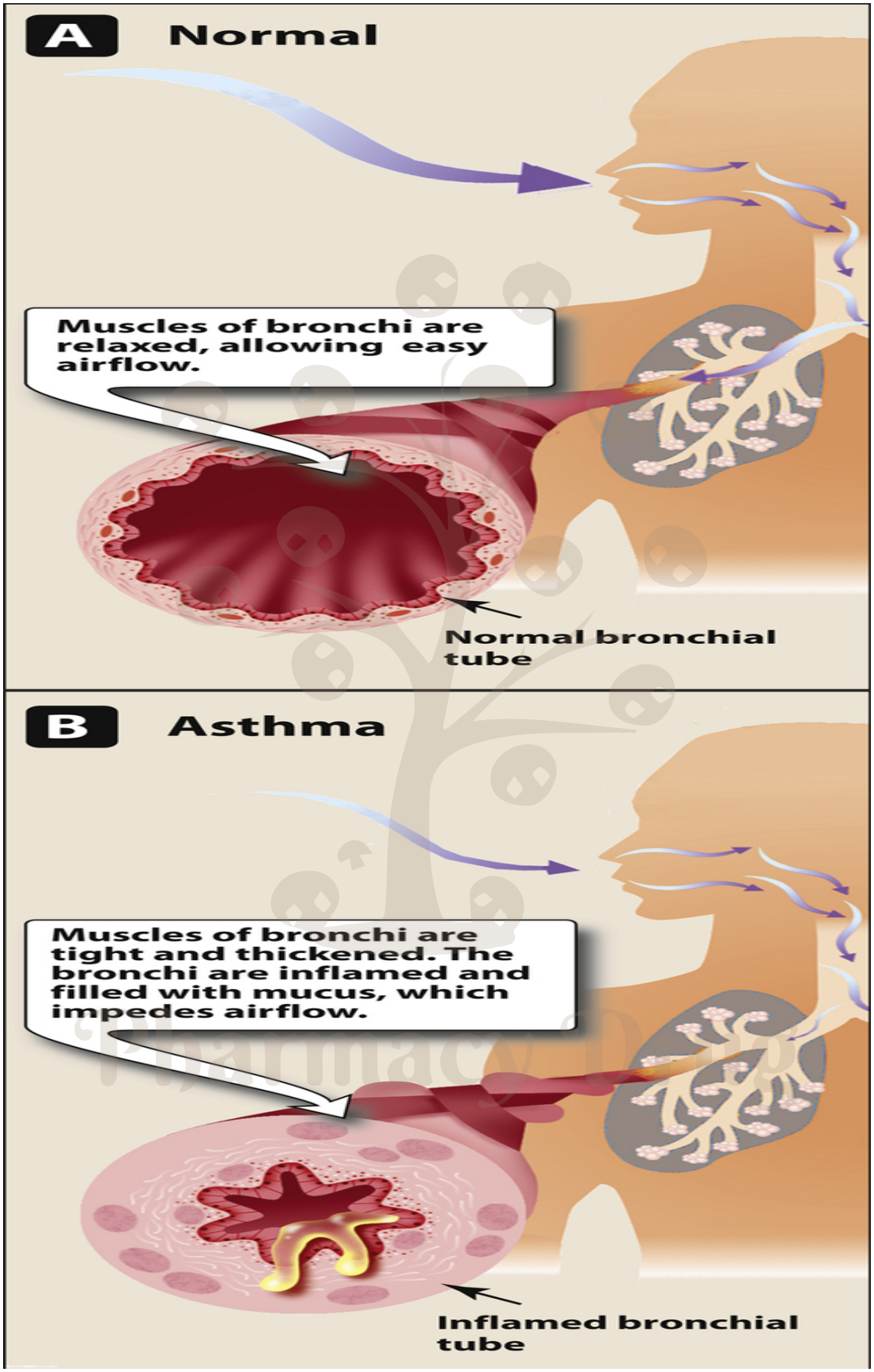

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Figure 41.2 Comparison of bronchi of normal and asthmatic individuals.

B. Goals of therapy

Drug therapy for long-term control of asthma is designed to reverse and prevent airway inflammation. The goals of asthma therapy are to decrease the intensity and frequency of asthma symptoms, prevent future exacerbations, minimize limitations in activity related to asthma symptoms, and minimize adverse effects. The Global Initiative for Asthma (GINA) guidelines recommend that all patients with asthma should receive treatment with a long-term controller medication and a reliever medication. Controller medications contain inhaled corticosteroids (ICSs) to reduce airway inflammation and the risk of asthma exacerbations. Reliever medications are used as needed for quick relief of symptoms during an asthma flare or exacerbation. First-line drug therapy based on frequency and severity of asthma symptoms is presented in Figure 41.3.

Asthma symptoms	Preferred treatment		Alternative treatment	
	Controller	Reliever	Controller	Reliever
Less than twice a month	Low-dose ICS-*formoterol* as needed		Use ICS whenever SABA is needed	SABA as needed
More than twice a month, but less than 4 to 5 days per week	Low-dose ICS-*formoterol* as needed		Low-dose maintenance ICS	SABA as needed
Most days of the week or awakening due to asthma at least once a week	Low-dose maintenance ICS-*formoterol*	Low-dose ICS-*formoterol* as needed	Low-dose maintenance ICS-LABA	SABA as needed
Daily symptoms or awakening due to asthma at least once a week; low lung function	Medium-dose maintenance ICS-*formoterol*	Low-dose ICS-*formoterol* as needed	Medium- or high-dose maintenance ICS-LABA	SABA as needed

Figure 41.3 Guidelines for the initial treatment of asthma in patients 12 years and older.ICS = inhaled corticosteroid; LABA = long-acting β_2 agonist; SABA = short-acting β_2 agonist.

C. Corticosteroids

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ICSs are the foundation of therapy for controller medications in patients with asthma (Figure 41.3). Corticosteroids (see Chapter 26) inhibit the release of arachidonic acid through inhibition of phospholipase A_2, thereby producing direct anti-inflammatory properties in the airways (Figure 41.4). To be most effective in controlling inflammation, these agents must be used regularly. In patients with mild asthma, as-needed use of ICS/*formoterol* for symptoms decreases the risk of severe asthma exacerbations. Treatment of exacerbations or severe asthma may require the addition of a short course of oral or intravenous corticosteroids.

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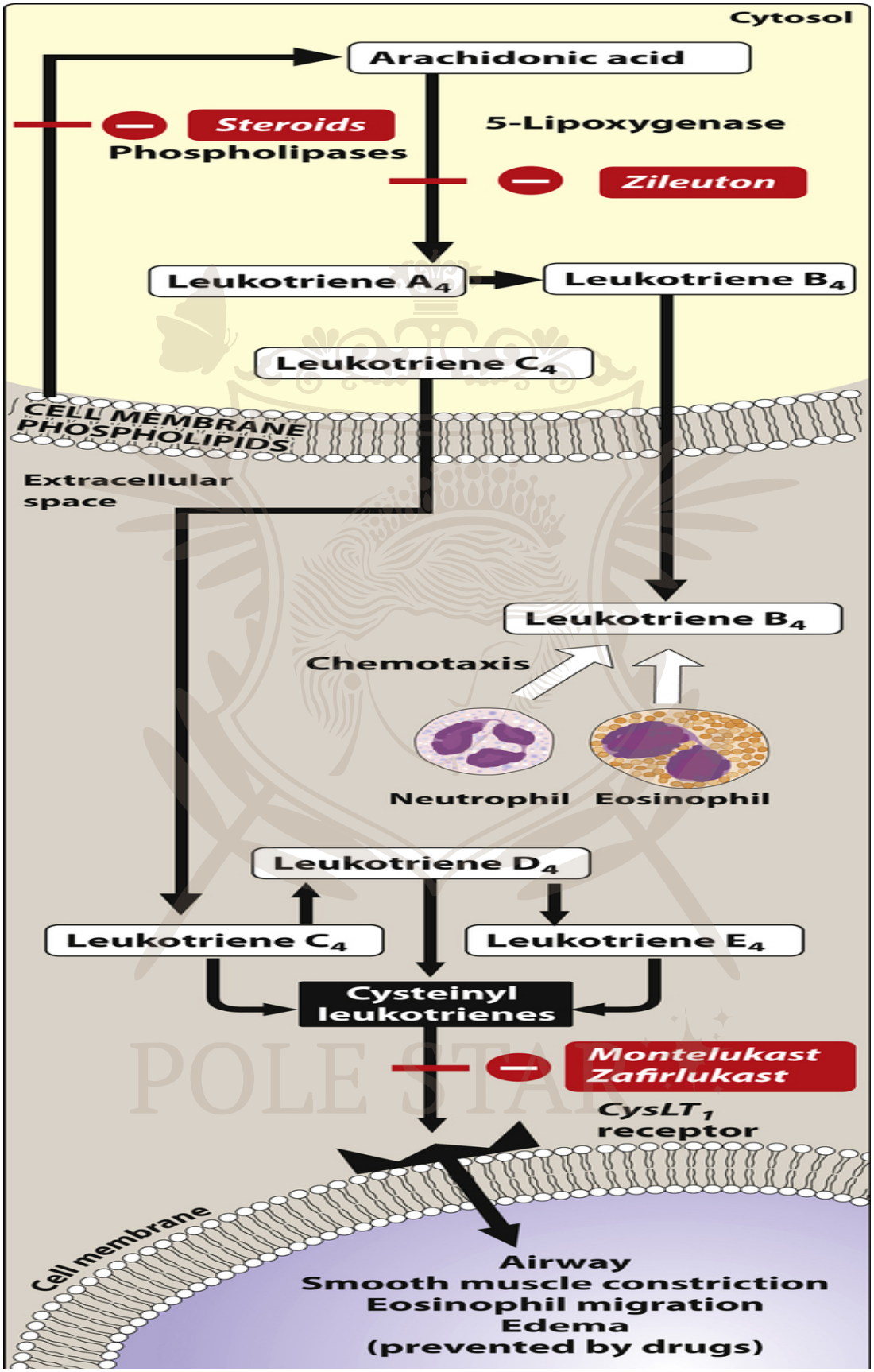
Cytosol
Arachidonic acid
Steroids
Phospholipases
5-Lipoxygenase
Zileuton
Leukotriene A4
Leukotriene B4
Leukotriene C4
CELL MEMBRANE PHOSPHOLIPIDS
Extracellular space
Leukotriene B4
Chemotaxis
Neutrophil
Eosinophil
Leukotriene D4
Leukotriene C4
Leukotriene E4
Cysteinyl leukotrienes
Montelukast
Zafirlukast
CysLT1 receptor
Cell membrane
Airway
Smooth muscle constriction
Eosinophil migration
Edema
(prevented by drugs)

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Figure 41.4 Sites of action for various respiratory medications.$CysLT_1$, cysteinyl leukotriene-1.

1.Actions on lung: ICS therapy directly targets underlying airway inflammation by decreasing the inflammatory cascade (eosinophils, macrophages, and T lymphocytes), reversing mucosal edema, decreasing the permeability of capillaries, and inhibiting the release of leukotrienes. After several months of regular use, ICSs reduce the hyperresponsiveness of the airway smooth muscle to a variety of bronchoconstrictor stimuli, such as allergens, irritants, cold air, and exercise.

2.Routes of administration

a. Inhalation: The development of ICS has markedly reduced the need for systemic corticosteroid treatment to achieve control of asthma symptoms. However, as with all inhaled medications, appropriate inhalation technique is critical to the success of therapy (see section on Inhaler Technique).

b. Oral/Systemic: Patients with a severe exacerbation of asthma (acute severe asthma, formerly called status asthmaticus) may require intravenous *methylprednisolone* or oral *prednisone* to reduce airway inflammation. In most cases, suppression of the hypothalamic–pituitary–adrenal cortex axis does not occur during the oral *prednisone* "burst" (short course) typically prescribed for an asthma exacerbation. Thus, a dose taper is unnecessary prior to discontinuation.

3.Adverse effects: Oral or parenteral corticosteroids have a variety of potentially serious adverse effects (see Chapter 26), whereas ICSs, particularly if used with a spacer device, have few systemic effects. ICS deposition on the oral and laryngeal mucosa can cause hoarseness and oropharyngeal

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candidiasis (due to local immune suppression). Patients should be instructed to rinse the mouth in a "swish-and-spit" method with water following use of the inhaler to decrease the chance of these adverse events. Also, use of a large volume spacer can limit the amount of drug deposited in the mouth, thus reducing the chances of oropharyngeal candidiasis (see section on Inhaler Technique). Due to the potential for serious adverse effects, chronic maintenance with oral corticosteroids should be reserved for patients who are not controlled on an ICS.

D. β_2-adrenergic agonists

Inhaled β_2-adrenergic agonists directly relax airway smooth muscle. They are used for the quick relief of asthma symptoms, as well as adjunctive therapy for long-term control of the disease.

1.Short-acting β_2 agonists: Short-acting β_2 agonists (SABAs) have a rapid onset of action (5-15 minutes) and provide relief for 3 to 6 hours. They are used for symptomatic treatment of bronchospasm, providing quick relief of acute bronchoconstriction. β_2 Agonists have no anti-inflammatory effects, and they should not be used as monotherapy for patients with persistent asthma. SABAs may be used for prevention of exercise-induced bronchospasm and should be administered on an as-needed basis. Direct-acting β_2-selective agonists include *albuterol* [al-BYOO-ter-all] and *levalbuterol* [leh-val-BYOO-ter-all]. These agents provide significant bronchodilation with little of the undesired effect of α or β_1 stimulation (see Chapter 6). Adverse effects, such as tachycardia, hyperglycemia, hypokalemia, hypomagnesemia, and β_2-mediated skeletal muscle tremors are minimized with inhaled delivery versus systemic administration.

2.Long-acting β_2 agonists: *Salmeterol* [sal-MEE-ter-all] and *formoterol* [for-MOE-ter-all] are long-acting β_2 agonists

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(LABAs) and chemical analogs of *albuterol. Salmeterol* and *formoterol* have a long duration of action, providing bronchodilation for at least 12 hours. [Note: *Formoterol* also has a rapid onset of action, rendering it useful for quick relief of symptoms.] Use of LABA monotherapy is contraindicated in asthma, and LABAs should be used only in combination with an asthma controller medication, such as an ICS. ICSs are the long-term controllers of choice, and LABAs are considered to be useful adjunctive therapy for attaining control of symptoms in asthma. Some LABAs are available as a combination product with an ICS (see Figure 41.1). Because of the rapid onset of *formoterol*, an ICS/*formoterol* combination (for example, *budesonide*/*formoterol*) can be used as both a daily controller medication and also for quick relief of asthma symptoms as needed. [Note: ICS/*formoterol* is the preferred reliever medication in asthma; SABAs are an alternative for quick relief of asthma symptoms; see Figure 41.3.] Adverse effects of LABAs are similar to quick-acting β_2 agonists.

Clinical Application 41.1: Downregulation of β_2 Adrenoceptors and Diminished Responsiveness to β_2 Adrenergic Agonists

β_2 Adrenoceptors (β_2 ARs) located on airway smooth muscles are G protein–-coupled receptors (see Chapter 2), subtype Gs. Upon activation by agonists such as SABAs and LABAs, these receptors lead to stimulation of the adenylyl cyclase enzyme, thereby increasing cellular cAMP levels and causing relaxation of airway smooth muscles. However, it has been observed that long-term treatment with these drugs leads to decreased bronchodilator response and tolerance secondary to internalization and downregulation of the β_2 AR.

The mechanism leading to development of tolerance results from phosphorylation of the receptor, causing activation of a group of protein kinase enzyme known as G protein–coupled receptor kinases (GRKs). GRKs phosphorylate the β_2 AR, thereby decreasing its ability to generate cAMP and increasing its affinity for a protein called β-arrestin. β-Arrestin causes internalization of β_2 AR, contributing to receptor desensitization and resulting in poor asthma control with chronic use of β_2 adrenergic agonists. This is one of

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the possible reasons that the Global Initiatives for Asthma (GINA) guidelines do not recommend the use of β_2 adrenergic agonists as monotherapy in the treatment of asthma.

III. ALTERNATIVE DRUGS USED TO TREAT ASTHMA

These drugs are useful for treatment of asthma in patients who are poorly controlled by conventional therapy or experience adverse effects secondary to corticosteroid treatment. These drugs should be used in conjunction with ICS therapy for most patients.

A. Leukotriene modifiers

Leukotrienes (LTs) B_4 and the cysteinyl leukotrienes, LTC_4, LTD_4, and LTE_4, are products of the 5-lipoxygenase pathway of arachidonic acid metabolism and part of the inflammatory cascade. 5-Lipoxygenase is found in cells of myeloid origin, such as mast cells, basophils, eosinophils, and neutrophils. LTB_4 is a potent chemoattractant for neutrophils and eosinophils, whereas the cysteinyl leukotrienes constrict bronchiolar smooth muscle, increase endothelial permeability, and promote mucus secretion. *Zileuton* [zye-LOO-ton] is a selective and specific inhibitor of 5-lipoxygenase, preventing the formation of both LTB_4 and the cysteinyl leukotrienes. *Zafirlukast* [za-FIR-loo-kast] and *montelukast* [mon-te-LOO-kast] are selective antagonists of the cysteinyl leukotriene-1 receptor, and they block the effects of cysteinyl leukotrienes (Figure 41.4). These agents are approved for the prevention of asthma symptoms. They should not be used in situations where immediate bronchodilation is required. Leukotriene receptor antagonists have also shown efficacy for the prevention of exercise-induced bronchospasm and *aspirin*-exacerbated respiratory disease (AERD). [Note: AERD is a condition characterized by asthma, nasal polyps, and

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development of respiratory symptoms following exposure to *aspirin* or other nonsteroidal anti-inflammatory drugs (NSAIDs).]

1.Pharmacokinetics: These agents are orally active and highly protein bound. Food impairs the absorption of *zafirlukast.* The drugs undergo extensive hepatic metabolism. *Zileuton* and its metabolites are excreted in urine, whereas *zafirlukast*, *montelukast*, and their metabolites undergo biliary excretion.

2.Adverse effects: Elevations in serum hepatic enzymes may occur with *zileuton* and *zafirlukast*, requiring periodic monitoring and discontinuation when enzymes exceed three to five times the upper limit of normal. Other effects include headache and dyspepsia. *Montelukast* contains a boxed warning regarding the potential for serious mental health symptoms such as agitation, depression, sleep disturbances, and suicidal ideations with use of this agent. A rare adverse event with *montelukast* and *zafirlukast* is eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome. The syndrome may include elevated eosinophils (eosinophilia), vasculitis, rash, muscle and joint pain, worsening respiratory symptoms, and neuropathy. Occurrence of EGPA may be associated with withdrawal of oral corticosteroid therapy. *Zafirlukast* is an inhibitor of cytochrome P450 (CYP) isoenzymes 2C8, 2C9, and 3A4, and *zileuton* inhibits CYP1A2. Coadministration with drugs that are substrates of these isoenzymes may result in increased effects and/or toxicity.

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B. Cromolyn

Cromolyn [KRO-moe-lin] is a prophylactic anti-inflammatory agent that inhibits mast cell degranulation and release of histamine. It is an alternative therapy for mild persistent asthma and is available as a nebulized solution. Because *cromolyn* is not a bronchodilator, it is not useful in managing an acute asthma attack. An intranasal

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formulation is used for treatment of allergic rhinitis and an oral formulation for systemic mastocytosis. Due to its short duration of action, this agent requires dosing three or four times daily, which affects adherence and limits its use. Adverse effects are minor and include cough, irritation, and unpleasant taste.

C. Cholinergic antagonists

The anticholinergic agents block vagally mediated contraction of airway smooth muscle and mucus secretion (see Chapter 5). Inhaled *ipratropium* [IP-ra-TROE-pee-um], a short-acting quaternary derivative of *atropine*, is not recommended for the routine treatment of acute bronchospasm in asthma, as its onset is much slower than that of inhaled SABAs. However, it may be useful in patients who are unable to tolerate a SABA or patients with asthma–COPD overlap syndrome. *Ipratropium* also offers additional benefit when used with a SABA for the treatment of acute asthma exacerbations in the emergency department. *Tiotropium* [tye-oh-TROE-pee-um], a long-acting anticholinergic agent, can be used as an add-on treatment in adult patients with severe asthma and a history of exacerbations. Adverse effects such as xerostomia and bitter taste are related to local anticholinergic effects.

D. Theophylline

Theophylline [thee-OFF-i-lin] is a methylxanthine bronchodilator that relieves airflow obstruction in chronic asthma and decreases asthma symptoms. It may also possess anti-inflammatory and immunomodulatory activity, although the exact mechanism of action is unclear. Previously, the mainstay of asthma therapy, *theophylline* has been replaced with β_2 agonists and corticosteroids and is rarely used due to its narrow therapeutic window, adverse effect profile, and potential for drug interactions. Overdose may cause seizures or potentially fatal arrhythmias. *Theophylline* is metabolized in the liver and is a CYP1A2 and 3A4 substrate. It is subject to numerous drug interactions. Serum

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concentration monitoring should be performed when *theophylline* is used chronically.

E. Monoclonal antibodies

Omalizumab [OH-ma-LIZ-ue-mab] is a monoclonal antibody that selectively binds to human immunoglobulin E (IgE). This leads to decreased binding of IgE to its receptor on the surface of mast cells and basophils. Reduction in surface-bound IgE limits the release of mediators of the allergic response. The monoclonal antibodies *mepolizumab* [MEP-oh-LIZ-ue-mab], *benralizumab* [ben-ra-LIZ-ue-mab], and *reslizumab* [res-LIZ-ue-mab] are interleukin-5 (IL-5) antagonists. IL-5 is the major cytokine involved in recruitment, activation, and survival of eosinophils in eosinophilic asthma. *Dupilumab* [doo-PIL-ue-mab] is a monoclonal antibody against interleukin-4 (IL-4) and interleukin-13 (IL-13). It acts by reducing the release of proinflammatory cytokines, chemokines, and IgE. These agents are indicated for add-on treatment of severe persistent asthma in patients who are poorly controlled with conventional therapy. Their use is limited by the high cost, route of administration (IV for *reslizumab* and subcutaneous for others), and adverse effect profile. Adverse effects include serious anaphylactic reactions (rare), arthralgias, fever, rash, and increased risk of infections. New malignancies have been reported.

IV. DRUGS USED TO TREAT CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is a chronic, irreversible obstruction of airflow that is usually progressive and characterized by persistent symptoms. These may include cough, excess mucus production, chest tightness, breathlessness, difficulty sleeping, and fatigue. Although symptoms are similar to asthma, the characteristic *irreversible* airflow

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obstruction of COPD is one of the most significant differences between the diseases. Smoking is the greatest risk factor for COPD and is directly linked to the progressive decline of lung function, as demonstrated by forced expiratory volume in one second (FEV_1). Smoking cessation should be recommended regardless of stage and severity of COPD or the age of patient. Drug therapy for COPD is aimed at relief of symptoms and prevention of disease progression. Unfortunately, with currently available care, many patients still experience a decline in lung function over time.

Clinical Application 41.2: Patient Assessment and Choice of Drug Therapy in COPD

Selection of drug therapy in stable COPD is primarily based on assessment of patient symptoms and the risk of future COPD exacerbations. Two common questionnaires used in the assessment of COPD symptoms include the Modified British Medical Research Council (mMRC) dyspnea questionnaire and the COPD Assessment Test (CAT). The mMRC assesses the level of breathlessness with certain activities, with a score range of 0 (breathless only with strenuous exercise) to 4 (breathless with simple activities such as dressing). The CAT evaluates dyspnea, as well as other symptoms, such as cough, level of mucus production, sleep, and overall energy level. The CAT score ranges from 0 to 40, with higher scores indicating a greater COPD symptom burden. Patients with an mMRC score of 2 or greater or a CAT score of 10 or greater are considered to have a higher symptom burden, whereas those with an mMRC score of 0 or 1 or a CAT score less than 10 are considered to have fewer COPD symptoms.

Assessment of the risk of future exacerbations is also important in the selection of drug therapy for stable COPD. Patients who have two or more moderate exacerbations (an exacerbation that requires treatment with short-acting bronchodilators, antibiotics, and/or oral corticosteroid therapy) or one severe exacerbation (requires hospitalization) in the past year are at higher risk of future exacerbations. Once the extent of symptoms and the risk of exacerbations have been characterized, the patient can be classified into one of four COPD groups (A, B, C, or D), and this classification is used to guide selection of drug therapy (Figure 41.5).

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Patient group	Risk of COPD exacerbation	Symptom burden	Recommended initial treatment
A	Low risk	Fewer symptoms	SABA or SAMA or LABA or LAMA
B	Low risk	More symptoms	LABA or LAMA
C	High risk	Fewer symptoms	LAMA
D	High risk	More symptoms	LAMA or LAMA + LABA or LABA + ICS

Figure 41.5 Guidelines for the pharmacologic therapy for stable chronic obstructive pulmonary disease.FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting β_2 agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting β_2 agonist; SAMA = short-acting muscarinic antagonist.

A. Bronchodilators

Inhaled bronchodilators, including the β_2-adrenergic agonists and anticholinergic agents (muscarinic antagonists), are the foundation of therapy for COPD (Figure 41.5). These drugs increase airflow, alleviate symptoms, and decrease exacerbations. As-needed use of a SABA (for example, *albuterol*) or a short-acting muscarinic antagonist (SAMA; for example, *ipratropium*) is appropriate for management of symptoms for patients in COPD group A (patients who have few symptoms and are at low risk of COPD exacerbations). The long-acting bronchodilators, LABAs, and long-acting muscarinic antagonists (LAMAs) are preferred as first-line treatment for all other COPD groups. LABAs include once-daily *indacaterol* [in-da-KA-ter-ol], *olodaterol* [OH-loe-DAT-er-ol], and *vilanterol* [vye-LAN-ter-ol], as well as the twice-daily inhaled formulations of *arformoterol*, *formoterol*, and *salmeterol. Aclidinium* [A-kli-DIN-ee-um], *tiotropium*, *glycopyrrolate* [GLYE-koe-PIR-oh-late], *revefenacin* [REV-e-FEN-a-sin], and *umeclidinium* [ue-ME-kli-DIN-ee-um]) are LAMAs. [Note: *Revefenacin* is only administered via a nebulizer. The other LAMAs are available in metered-dose or dry powder

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inhaler formulations.] The combination of a LAMA and a LABA may be helpful in patients who have inadequate response to a single inhaled bronchodilator and are at risk of exacerbations. All patients with COPD should have a short-acting bronchodilator included in the treatment regimen for quick relief of symptoms.

B. Corticosteroids

The addition of an ICS to a long-acting bronchodilator may improve symptoms, lung function, and quality of life in COPD patients with a history of hospitalizations for COPD, or those with one or more moderate COPD exacerbations per year, higher eosinophil counts, or symptoms of both asthma and COPD. However, ICS treatment in COPD should be restricted to these patients, since use is associated with an increased risk of pneumonia. Although often used for acute exacerbations, oral corticosteroids are not recommended for long-term treatment of COPD.

C. Other agents

Roflumilast [roe-FLUE-mi-last] is an oral phosphodiesterase-4 inhibitor used to reduce exacerbations in patients with severe chronic bronchitis. Although its activity in COPD is not well defined, it is theorized to reduce inflammation by increasing levels of intracellular cAMP in lung cells. *Roflumilast* is not a bronchodilator and is not indicated for the relief of acute bronchospasm. It is indicated in patients with chronic bronchitis who experience exacerbations on LABA/LAMA combination therapy or those with exacerbations on LABA/LAMA/ICS therapy. [Note: For patients treated with LABA/LAMA therapy and higher eosinophil counts or concomitant symptoms of asthma, addition of an ICS may be preferred over *roflumilast.* Addition of *roflumilast* to LABA/LAMA therapy is recommended for patients with lower eosinophil counts (for example, <100 cells/μL). Addition of the macrolide *azithromycin* is an alternative to *roflumilast* in nonsmokers who have exacerbations while treated with LABA/LAMA or LABA/LAMA/ICS therapy.] Use of *roflumilast* is

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limited by common adverse effects including weight loss, nausea, diarrhea, and headache. In COPD, the use of *theophylline* has largely been replaced by the more effective and tolerable long-acting bronchodilators.

V. INHALER TECHNIQUE

Appropriate inhaler technique differs between metered-dose inhalers (MDIs) and dry powder inhalers (DPIs). Proper technique is critical to the success of therapy, and inhaler technique should be assessed regularly.

A. Metered-dose inhalers and dry powder inhalers

MDIs have propellants that eject the active medication from the canister. Patients should be instructed to exhale before they actuate the inhaler, and then begin to inhale *slowly* as they press the canister and continue inhaling *slowly* and *deeply* throughout actuation. This technique avoids impaction of the medication onto the laryngeal mucosa and facilitates the drug reaching the site of action in the bronchial smooth muscle. A large fraction (typically 80%-90%) of inhaled medication (for example, corticosteroids) is either deposited in the mouth and pharynx or swallowed (Figure 41.6). The remaining 10% to 20% of a dose of inhaled glucocorticoids that is not swallowed reaches the site of action in the airway. Use of appropriate technique with ICS reduces the risk of systemic absorption and adverse effects. DPIs require a different inhaler technique. Patients should be instructed to inhale *quickly* and *deeply* to optimize drug delivery to the lungs. Patients using any type of inhaled corticosteroid device should be instructed to rinse the mouth after use to prevent the development of oral candidiasis.

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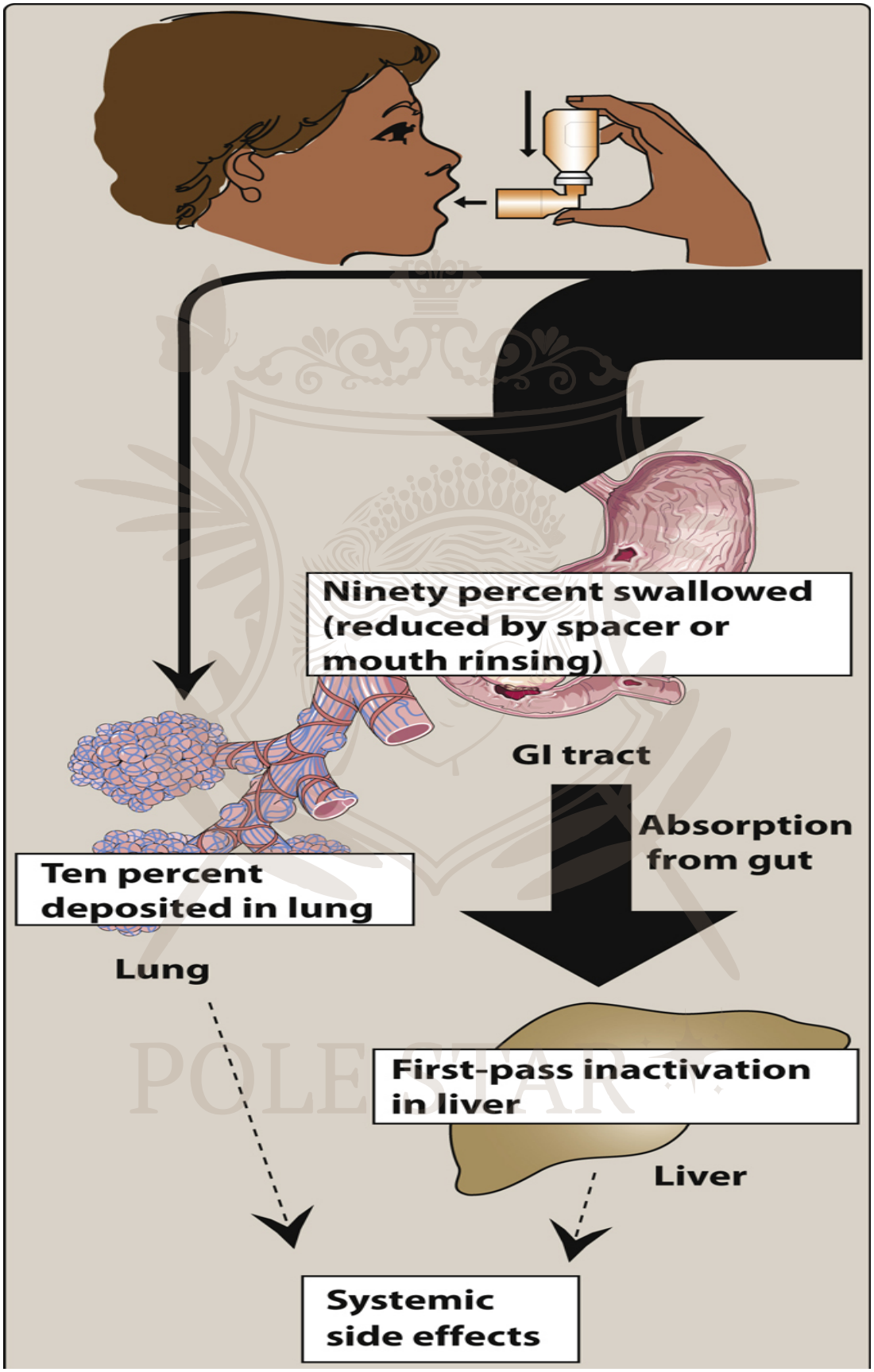
Ninety percent swallowed (reduced by spacer or mouth rinsing)
GI tract
Absorption from gut
Ten percent deposited in lung
Lung
First-pass inactivation in liver
Liver
Systemic side effects

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Figure 41.6 Pharmacokinetics of inhaled glucocorticoids.GI = gastrointestinal.

B. Spacers

A spacer is a large-volume chamber attached to an MDI. The chamber reduces the velocity of the aerosol before entering the mouth, allowing large drug particles to be deposited in the device. The smaller, higher-velocity drug particles are less likely to be deposited in the mouth and more likely to reach the target airway tissue (Figure 41.7). Patients should be advised to wash and/or rinse spacers to reduce the risk of bacterial or fungal growth that may induce an asthma attack.

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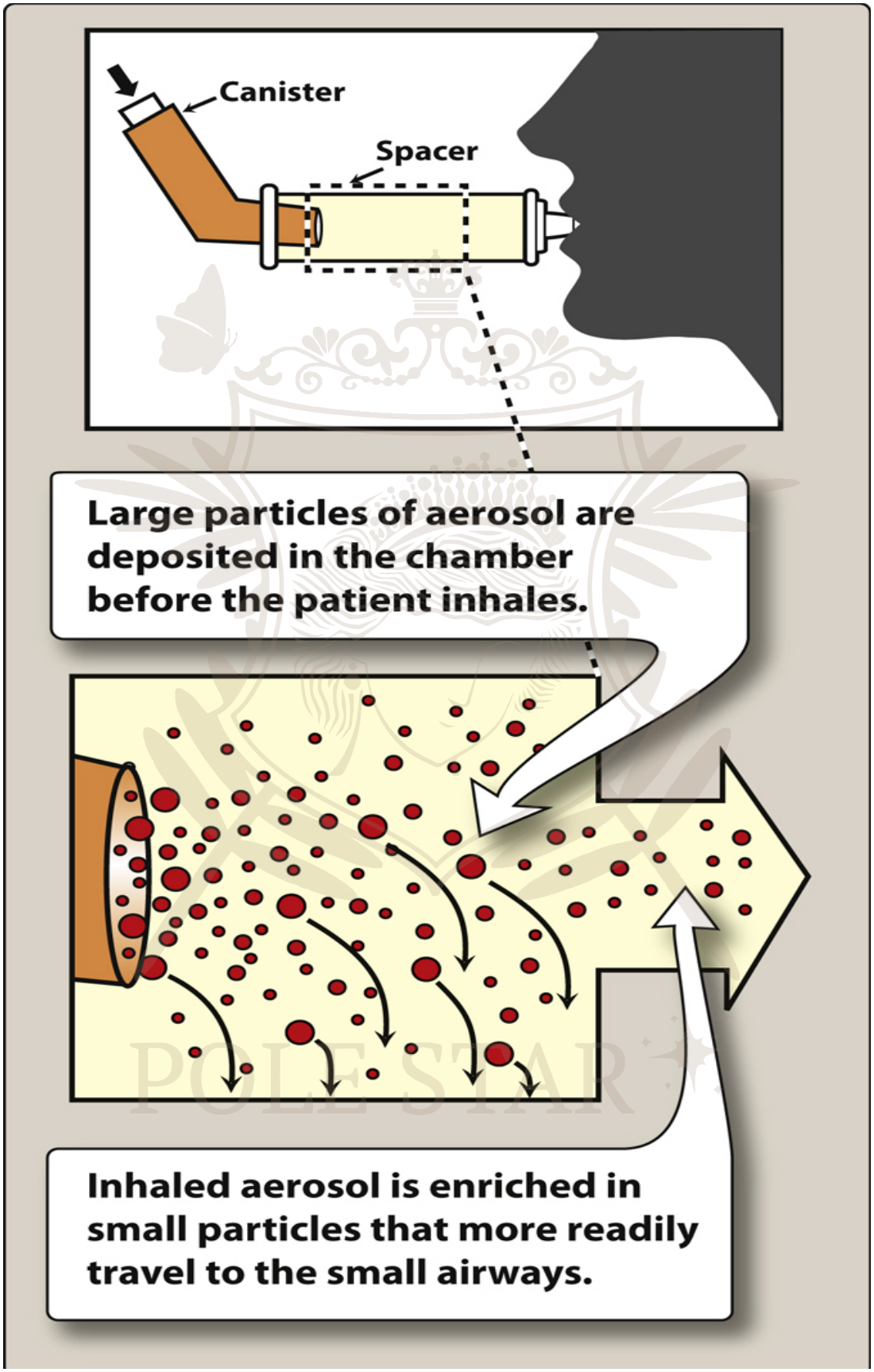
Canister
Spacer
Large particles of aerosol are deposited in the chamber before the patient inhales.
Inhaled aerosol is enriched in small particles that more readily travel to the small airways.

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Figure 41.7 Effect of a spacer on the delivery of an inhaled aerosol.

VI. DRUGS USED TO TREAT ALLERGIC RHINITIS

Rhinitis is an inflammation of the mucous membranes of the nose and is characterized by sneezing, itchy nose/eyes, watery rhinorrhea, nasal congestion, and sometimes a nonproductive cough. An attack may be precipitated by inhalation of an allergen (such as dust, pollen, or animal dander). The foreign material interacts with mast cells coated with IgE generated in response to a previous allergen exposure. The mast cells release mediators, such as histamine, leukotrienes, and chemotactic factors that promote bronchiolar spasm and mucosal thickening from edema and cellular infiltration. Antihistamines and/or intranasal corticosteroids are preferred therapies for allergic rhinitis.

A. Antihistamines

Oral antihistamines (H_1 receptor antagonists; see Chapter 39) have a fast onset of action and are useful for the management of symptoms of allergic rhinitis caused by histamine release, such as sneezing, watery rhinorrhea, and itchy eyes/nose. However, they are more effective for prevention of symptoms in mild or intermittent disease, rather than treatment once symptoms have begun. First-generation antihistamines, such as *diphenhydramine* and *chlorpheniramine*, are usually not preferred due to adverse effects, such as sedation, performance impairment, and other anticholinergic effects. The second-generation antihistamines (for example, *fexofenadine*, *loratadine*, *desloratadine*, *cetirizine, levocetirizine*) are generally better tolerated. Ophthalmic and nasal antihistamine delivery devices are available for targeted, topical tissue delivery. Examples of topical intranasal

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antihistamines include *olopatadine* [OH-loe-PA-ta-deen] and *azelastine* [a-ZEL-uh-steen]. Intranasal antihistamines provide increased delivery of the drug with fewer adverse effects. Combinations of antihistamines with decongestants (see below) are effective when congestion is a feature of rhinitis, or when patients have no response or incomplete control of symptoms with intranasal corticosteroids.

B. Corticosteroids

Intranasal corticosteroids, such as *beclomethasone*, *budesonide*, *fluticasone*, *ciclesonide*, *mometasone*, and *triamcinolone*, are the most effective medications for treatment of allergic rhinitis. With an onset of action that ranges from 3 to 36 hours after first dose, intranasal corticosteroids improve sneezing, itching, rhinorrhea, and nasal congestion. Systemic absorption is minimal, and adverse effects of treatment are localized. These include nasal irritation, nosebleed, sore throat, and, rarely, candidiasis. To minimize systemic absorption, patients should be instructed to avoid deep inhalation during administration into the nose, because the target tissue is the nose, not the lungs or the throat. For patients with chronic rhinitis, improvement may not be seen until 1 to 2 weeks after starting therapy.

C. α-adrenergic agonists

Short-acting α-adrenergic agonists (“nasal decongestants”), such as *phenylephrine*, constrict dilated arterioles in the nasal mucosa and reduce airway resistance (see Chapter 6) to help reduce symptoms of allergic rhinitis. Longer-acting *oxymetazoline* [OX-i-me-TAZ-oh-leen] is also available. While these agents manage the acute symptoms of allergic rhinitis, they do not help prevent recurrence of symptoms. When administered intranasally, these drugs have a rapid onset of action and show few systemic effects. However, intranasal formulations of α-adrenergic agonists should be used for no longer than 3 days due to the risk of rebound nasal congestion (rhinitis medicamentosa). For this reason, the α-adrenergic agents are not used in the long-term treatment of

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allergic rhinitis. Administration of oral α-adrenergic agonists results in not only a longer duration of action but also increased systemic effects, such as increased blood pressure and heart rate (see Chapter 6). As with intranasal formulations, regular use of oral α-adrenergic agonists (*phenylephrine* and *pseudoephedrine*) alone or in combination with antihistamines is not recommended.

D. Other agents

Intranasal *cromolyn* may be useful in allergic rhinitis, particularly when administered before contact with an allergen. To optimize the therapeutic effect, dosing should begin at least 1 to 2 weeks prior to allergen exposure. Although potentially inferior to other treatments, some leukotriene receptor antagonists (for example, *montelukast*) are effective for allergic rhinitis as monotherapy or in combination with other agents. *Montelukast* may be a reasonable option in patients who also have asthma. An intranasal formulation of *ipratropium* is available to treat rhinorrhea associated with allergic rhinitis or the common cold. It does not relieve sneezing or nasal congestion.

VII. DRUGS USED TO TREAT COUGH

Coughing is an important defense mechanism of the respiratory system in response to irritants and is a common reason for patients to seek medical care. A troublesome cough may represent several etiologies, such as the common cold, sinusitis, or an underlying chronic respiratory disease. In some cases, cough may be an effective defense reflex against an underlying bacterial infection and should not be suppressed. Before treating cough, identification of its cause is important to ensure that antitussive treatment is appropriate. The priority should always be to treat the underlying cause of cough when possible. This may require antibiotic therapy. Drugs used to suppress cough are classified as antitussives, and drugs used to help clear mucus from the airways in patients with a productive cough are expectorants.

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A. Opioids

Codeine [KOE-deen], an opioid, decreases the sensitivity of cough centers in the central nervous system to peripheral stimuli. These therapeutic effects occur at doses lower than those required for analgesia. However, common adverse effects, such as constipation, dysphoria, and fatigue, still occur. In addition, *codeine* has addictive potential, which limits its use, given increasing concerns with opioid addiction globally (see Chapter 21). *Dextromethorphan* [dex-troe-meth-OR-fan] is a synthetic derivative of *morphine* that has no analgesic effects in antitussive doses. In addition to blocking the medullary cough center reflex, it also blocks the *N*-methyl-d-Aspartate (NMDA) excitatory receptors in the central nervous system. It has a better adverse effect profile than does *codeine* and is equally effective for cough suppression. In low doses, *dextromethorphan* has little risk for addiction. However, it is also a potential drug of abuse, since it may cause dysphoria at high doses. Opioid antitussives have a potential to cause serotonin syndrome when coadministered with serotonergic drugs.

B. Benzonatate

Unlike the opioids, *benzonatate* [ben-ZOE-na-tate], chemically similar to local anesthetics *tetracaine* and *benzocaine*, suppresses the cough reflex through peripheral action. It anesthetizes the stretch receptors located in the respiratory passages, lungs, and pleura. Adverse effects include dizziness and numbness of the tongue, mouth, and throat. These localized effects may be particularly problematic if the capsules are broken or chewed and the drug comes in direct contact with the oral mucosa. Patients should take the drug with plenty of water and swallow immediately without chewing to avoid these adverse effects.

C. Guaifenesin

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Guaifenesin [gwye-FEN-e-sin], an expectorant, is available as a single-ingredient formulation and is commonly found in combination cough products with *codeine* or *dextromethorphan.* It reduces mucus viscosity and loosens mucus in the airways, thereby enhancing the mucociliary clearance of sputum. Administration of *guaifenesin* changes a dry cough to a productive cough, allowing the patient to clear the mucus. Adverse effects include gastrointestinal disturbances, dizziness, headache, and skin rash. Kidney stone formation is possible with excessive use or abuse of drug formulations containing *guaifenesin.*

D. Acetylcysteine

Acetylcysteine reduces sputum viscosity by splitting the disulfide bonds of viscous mucoproteins. It is administered orally for COPD. An intravenous formulation is also used as an antidote in *acetaminophen* poisoning (see Chapter 46). Adverse effects associated with oral administration include nausea, vomiting, and stomatitis. Intravenous injections can cause rash, drug fever, itch and, rarely, anaphylactic reactions. Inhaled *acetylcysteine* is no longer recommended in the treatment of COPD or cystic fibrosis due to the potential for reflex bronchospasm when the drug is inhaled. *Acetylcysteine* has a strong unpleasant odor of rotten eggs due to sulfhydryl groups it contains, making the drug unpalatable. Hence, it is mixed with cola or fruit juice for oral administration.

E. Dornase alfa

Dornase alfa is a purified recombinant human deoxyribonuclease, an enzyme that hydrolyzes deoxyribonucleic acid (DNA). Patients with cystic fibrosis (CF) have viscous purulent secretions in the airways, resulting in sputum that is difficult to clear. The viscosity of secretions is due, in part, to DNA released from leukocytes that accumulate in response to pulmonary infections in CF. *Dornase alfa* cleaves extracellular DNA present in purulent pulmonary secretions, thereby reducing sputum viscosity in patients with CF. The drug is administered once daily via a nebulizer. Adverse

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effects include voice changes, pharyngitis, laryngitis, rhinitis, and chest pain.

Chapter Summary

- All patients with asthma should receive treatment with a controller medication and a reliever medication. Controller medications contain inhaled corticosteroids (ICSs) to reduce airway inflammation and the risk of asthma exacerbations. Reliever medications are used as needed for quick relief of symptoms during an asthma flare or exacerbation.
- Inhaled corticosteroids (ICSs) target the underlying airway inflammation in asthma. Patients should be instructed to rinse the mouth in a "swish-and-spit" method with water following use of ICS to reduce the risk of oral candidiasis and hoarseness.
- Inhaled β_2-adrenergic agonists directly relax airway smooth muscle. Short-acting β_2 agonists (SABAs; *albuterol* or *levalbuterol*) are used for quick relief of symptoms in asthma.
- Long-acting β_2 agonists (LABAs; *salmeterol*, *formoterol*) provide bronchodilation for at least 12 hours. Monotherapy with LABAs is contraindicated in asthma, and these agents should be used in combination with ICS.
- Because of the rapid onset of *formoterol*, an ICS/*formoterol* combination can be used as both a daily controller medication and also for quick relief of asthma symptoms as needed. ICS/*formoterol* is the preferred reliever medication for the treatment of asthma.
- Mast cell stabilizers, leukotriene modifiers and monoclonal antibodies are add-on therapies in patients with asthma who are either inadequately controlled or unable to tolerate ICS.
- Unlike asthma, COPD is characterized by progressive irreversible airflow obstruction. The mainstay of treatment of most stages of COPD is long-acting muscarinic antagonists (LAMAs; *aclidinium*, *glycopyrrolate*, *tiotropium*, or *umeclidinium*) and/or LABAs.
- All patients with COPD should have a SABA included in the treatment regimen for quick relief of symptoms.
- *Roflumilast* is an oral phosphodiesterase-4 inhibitor used to reduce exacerbations in patients with chronic bronchitis on standard therapy (LABA/LAMA).
- Systemic corticosteroids are useful in the treatment of severe exacerbations of asthma or COPD not responding adequately to other treatments.

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- Intranasal corticosteroids (for example, *beclomethasone*, *budesonide*, *fluticasone*, *ciclesonide*, *mometasone*, and *triamcinolone*) are the most effective medications for treatment of allergic rhinitis.
- The symptoms of allergic rhinitis can also be managed with second-generation antihistamines (H_1 receptor antagonists), although these agents are more effective in preventing than treating symptoms.
- Depending on the mechanism of action, the drugs used in treatment of cough are classified as antitussives (cough suppressants) or expectorants (mucoactive agents).
- Antitussives (*codeine*, *dextromethorphan*, *benzonatate*) suppress a dry nonproductive cough, and expectorants (*guaifenesin*) are used to enhance sputum clearance by decreasing its viscosity and/or increasing production.

STUDY QUESTIONS

Choose the ONE best answer.

41.1A 22-year-old woman with asthma goes hiking with her friends on a cold, windy day. While hiking, she suddenly experiences difficulty in breathing, dry cough, and chest tightness. Which of the following drugs can provide prompt relief of her symptoms?

A. Inhaled fluticasone
B. Inhaled beclomethasone
C. Inhaled albuterol
D. Inhaled salmeterol

Correct answer = C. Inhalation of a SABA with a rapid onset, such as albuterol, usually provides quick relief of symptoms. Inhaled budesonide/formoterol would also be an excellent option. Although it is a LABA, formoterol has a rapid onset of action. Inclusion of the inhaled corticosteroid budesonide will help reduce the risk of future exacerbations. Inhaled corticosteroids such as beclomethasone and fluticasone are effective long-term controller medications to treat chronic airway inflammation but do not provide any immediate effect for bronchospasm when used as single agents. Salmeterol is a long-acting β_2 agonist, and the onset of action is delayed. It should not be used for quick relief of symptoms.

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41.2 A patient with asthma complains of increasing frequency of asthma attacks. He has been using an albuterol inhaler when he has symptoms. However, this is not helping him much lately, and he is suffering from daily asthma symptoms. Which of the following is the most appropriate for management of asthma in this patient?

A. Add salmeterol
B. Add oral prednisone
C. Change albuterol to budesonide/formoterol
D. Change albuterol to salmeterol

Correct answer = C. A patient who is inadequately controlled with inhaled albuterol needs an ICS-containing controller treatment to reduce symptoms and the risk of asthma exacerbation. Budesonide/formoterol is an ICS/LABA combination that can be used on as-needed basis or as a daily controller medication, depending on the frequency and severity of symptoms. Oral prednisone would be considered if the patient does not improve with addition of an ICS to the regimen and if he is having acute severe symptoms. Monotherapy with a LABA (salmeterol) is contraindicated in asthma. If used, salmeterol should be used with an ICS.

41.3 During a dental cleaning, a patient with asthma is noted to have white patches in his oral cavity, which can be easily scraped off. He states that the lesions appeared after he was started on a new inhaler for controlling his worsening asthma. Which of the following drugs most likely contributed to the symptoms this patient?

A. Beclomethasone
B. Cromolyn
C. Levalbuterol
D. Zileuton

Correct answer = A. Inhaled corticosteroids such as beclomethasone are associated with development of oropharyngeal candidiasis due to a local immunosuppressant effect. Levalbuterol, cromolyn, and zileuton are not associated with oropharyngeal candidiasis.

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41.4 A 68-year-old man has COPD with moderate airway obstruction. Despite using salmeterol twice daily, he reports continued symptoms of shortness of breath with mild exertion. Which of the following agents is the most appropriate addition to his current therapy?

A. Systemic corticosteroids
B. Albuterol
C. Tiotropium
D. Roflumilast

Correct answer = C. The addition of an anticholinergic bronchodilator to the LABA salmeterol would be appropriate and provide additional therapeutic benefit. Systemic corticosteroids are used to treat exacerbations in patients with COPD but not recommended for chronic use. The addition of a SABA (albuterol) is less likely to provide additional benefit since the patient is already using medication with the same mechanism of action. Roflumilast is not indicated, since the patient is not reporting exacerbations and only has moderate airway obstruction.

41.5 A 56-year-old man is newly diagnosed with COPD. During the last year he has had two respiratory illnesses that required treatment with antibiotics and an inhaler. His COPD Assessment Test score is 9, and the provider categorizes the COPD as group C. Which of the following is the most appropriate treatment for this patient?

A. Formoterol/glycopyrrolate
B. Indacaterol
C. Salmeterol/fluticasone
D. Tiotropium

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Correct answer = D. A LAMA (tiotropium) is the preferred treatment for COPD group C. Patients in group C have a lower COPD symptom burden but are at higher risk of future exacerbations. Monotherapy with a LABA (indacaterol) could be considered for patients in group A or B. A combination of LABA/LAMA (formoterol/glycopyrrolate) could be a next step if the patient does not respond

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to tiotropium. A LABA/ICS combination (salmeterol/fluticasone) is recommended for certain patients in group D (for example, those with higher eosinophil counts).

41.6 Which of the following therapeutic options for COPD acts by inhibiting phosphodiesterase-4?

A. Dupilumab
B. Roflumilast
C. Salmeterol
D. Tiotropium

Correct answer = B. Roflumilast is a PDE-4 inhibitor. Dupilumab is a monoclonal antibody against interleukin-4 (IL-4) and interleukin-13 (IL-13). It is indicated for the treatment of asthma. Salmeterol is a long-acting β_2-adrenergic agonist (LABA), and tiotropium is a long-acting muscarinic antagonist (LAMA).

41.7 A 32-year-old man with a history of opioid addiction presents with cough due to a viral upper respiratory system infection. Which of the following treatments is appropriate symptomatic treatment of cough in this patient?

A. Guaifenesin/dextromethorphan
B. Guaifenesin/codeine
C. Benzonatate
D. Montelukast

Correct answer = C. Benzonatate suppresses the cough reflex through peripheral action and has no abuse potential. Dextromethorphan, an opioid derivative, and codeine, an opioid, both have abuse potential. Montelukast is not indicated for cough suppression.

41.8 A patient complains of chest tightness and difficulty breathing after taking aspirin or other NSAIDs. Examination reveals nasal polyps and increased eosinophils on differential white blood cell count. Which of the following drugs would be most appropriate to control his symptoms?

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A. Albuterol
B. Oxymetazoline
C. Roflumilast
D. Zileuton

Correct answer = D. The patient suffers from aspirin-exacerbated respiratory disease (AERD). Zileuton, an antileukotriene drug, is the most appropriate choice to control his symptoms, which are secondary to excess leukotriene production following administration of NSAIDs. Albuterol is a short-acting β_2-adrenergic agonist (SABA) used to relieve symptoms of an acute asthma attack. Roflumilast is an agent for treatment of COPD, and oxymetazoline is a nasal decongestant used for short-term management of symptoms of allergic rhinitis.

41.9 Which category of allergic rhinitis medications is most likely to be associated with rhinitis medicamentosa (rebound nasal congestion) with prolonged use?

A. Intranasal corticosteroid
B. Intranasal decongestant
C. Leukotriene antagonist
D. Oral antihistamine

Correct answer = B. Intranasal decongestants should be used no longer than 3 days due to the risk of rebound nasal congestion (rhinitis medicamentosa). For this reason, the α-adrenergic agents should not be used in the long-term treatment of allergic rhinitis. The other agents may be used as chronic therapies.

41.10 A 25-year-old woman complains of symptoms of allergic rhinitis, including excessive sneezing and itchy and runny nose. Which of the following medications would be most useful in this case?

A. Cromolyn
B. Fluticasone
C. Ipratropium
D. Montelukast

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Correct answer = B. Intranasal corticosteroids such as fluticasone are the most effective therapy for symptoms of allergic rhinitis. Symptoms can also be prevented with H_1 receptor antagonists. Cromolyn is a mast cell stabilizer. Intranasal cromolyn can be used to prevent attacks of allergic rhinitis, although it is not as effective as corticosteroids. Ipratropium is useful to reduce rhinorrhea (runny nose), but it does not help with sneezing. Montelukast is a less effective agent in the treatment of allergic rhinitis.

POLE STAR

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42

Gastrointestinal and Antiemetic Drugs

Carol Motycka, Adonice Khoury

I. OVERVIEW

This chapter describes drugs used to treat six common medical conditions involving the gastrointestinal (GI) tract: (1) peptic ulcers and gastroesophageal reflux disease (GERD), (2) chemotherapy-induced emesis, (3) diarrhea, (4) constipation, (5) irritable bowel syndrome (IBS), and (6) and inflammatory bowel disease (IBD). Many drugs described in other chapters also find application in the treatment of GI disorders. For example, the *meperidine* derivative *diphenoxylate*, which decreases peristaltic activity of the gut, is useful in the treatment of severe diarrhea. Other drugs are used almost exclusively to treat GI tract disorders. For example, H_2 receptor antagonists and proton pump inhibitors (PPIs) are used to heal peptic ulcers.

II. DRUGS USED TO TREAT PEPTIC ULCER DISEASE AND GASTROESOPHAGEAL REFLUX DISEASE

The two main causes of peptic ulcer disease are infection with gram-negative Helicobacter pylori and the use of nonsteroidal anti-

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inflammatory drugs (NSAIDs). Increased hydrochloric acid (HCl) secretion and inadequate mucosal defense against gastric acid also play a role. Treatment approaches include (1) eradicating the H. pylori infection, (2) reducing secretion of gastric acid with the use of PPIs or H_2 receptor antagonists, and/or (3) providing agents that protect the gastric mucosa from damage, such as *misoprostol* and *sucralfate.* Figure 42.1 summarizes agents that are effective in treating peptic ulcer disease.

POLE STAR

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ANTIMICROBIAL AGENTS

Amoxicillin GENERIC ONLY
Bismuth compounds PEPTO-BISMOL
Clarithromycin BIAXIN
Metronidazole FLAGYL
Tetracycline GENERIC ONLY

H_2 – HISTAMINE RECEPTOR BLOCKERS

Cimetidine TAGAMET
Famotidine PEPCID
Nizatidine AXID

PROTON PUMP INHIBITORS

Dexlansoprazole DEXILANT
Esomeprazole NEXIUM
Lansoprazole PREVACID
Omeprazole PRILOSEC
Pantoprazole PROTONIX
Rabeprazole ACIPHEX

PROSTAGLANDINS

Misoprostol CYTOTEC

ANTACIDS

Aluminum hydroxide GENERIC ONLY
Calcium carbonate TUMS
Magnesium hydroxide MILK OF MAGNESIA

MUCOSAL PROTECTIVE AGENTS

Bismuth subsalicylate PEPTO-BISMOL
Sucralfate CARAFATE

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Figure 42.1 Summary of drugs used to treat peptic ulcer disease and gastroesophageal reflux disease.

A. Antimicrobial agents

Patients with peptic ulcer disease (duodenal or gastric ulcers) who are infected with H. pylori require antimicrobial treatment. Infection with H. pylori is diagnosed via endoscopic biopsy of the gastric mucosa or with various noninvasive methods, including serology, fecal antigen tests, and urea breath tests (Figure 42.2). Figure 42.3 shows a biopsy sample in which *H. pylori* is discovered on the gastric mucosa. Eradication of H. pylori with various combinations of antimicrobial drugs results in rapid healing of active ulcers and low recurrence rates (less than 15%, compared with 60%–100% per year for ulcers healed with acid-reducing therapy alone). Currently, quadruple therapy of *bismuth subsalicylate*, *metronidazole*, and *tetracycline* plus a PPI is a recommended first-line option. This usually results in a 90% or greater eradication rate. Triple therapy consisting of a PPI combined with *amoxicillin* (*metronidazole* may be used in *penicillin*-allergic patients) plus *clarithromycin* is a preferred treatment when rates of *clarithromycin* resistance are low and the patient has no prior exposure to macrolide antibiotics.

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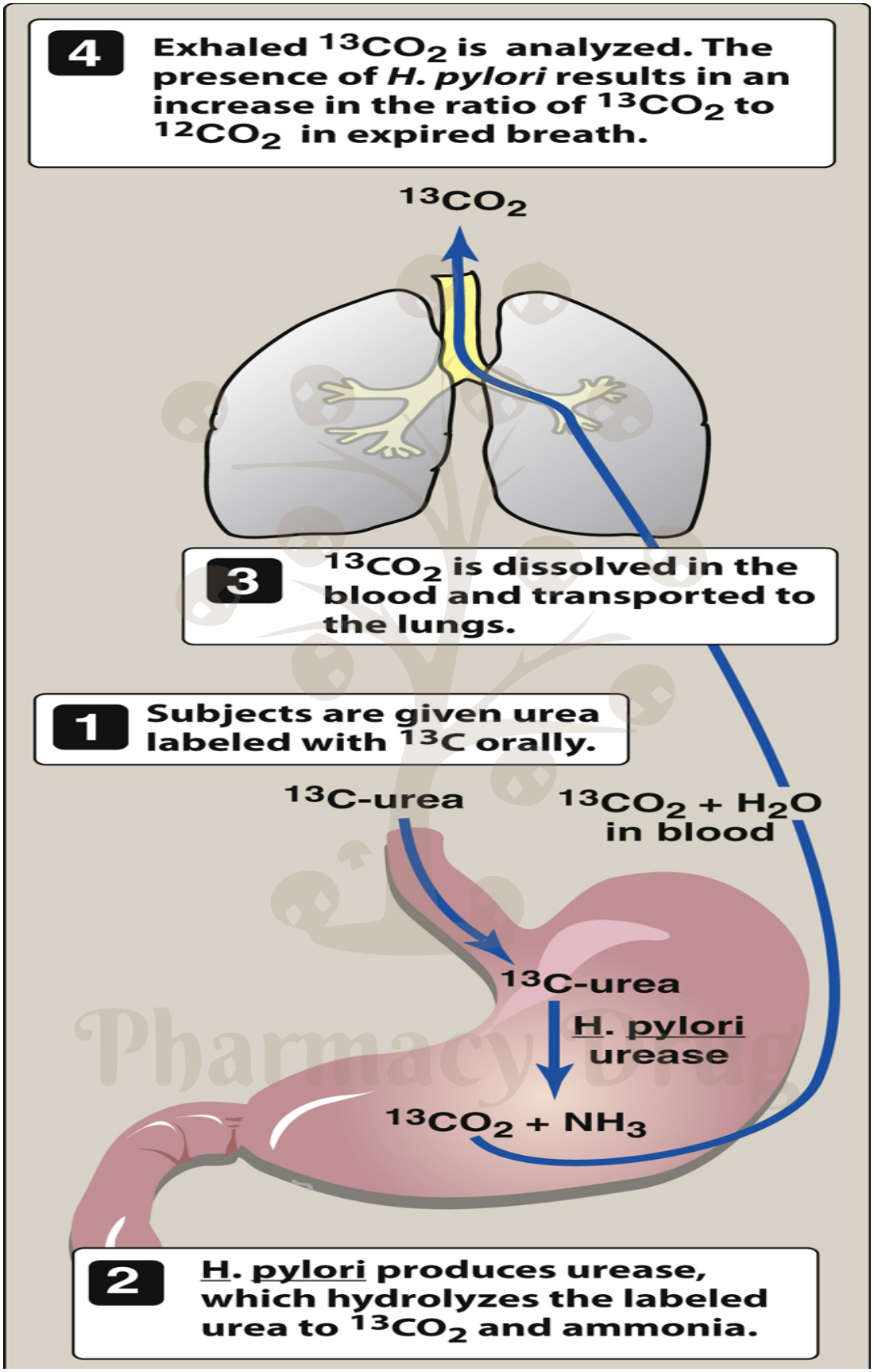

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Figure 42.2 Urea breath test, one of several noninvasive methods for detecting presence of Helicobacter pylori.Modified from D. R.Cave . Therapeutic approaches to recurrent peptic ulcer disease. *Hosp. Pract*. 27(9A): 33–49, 199 (1992). With permission from Taylor & Francis Ltd, www.tandfonline.com.

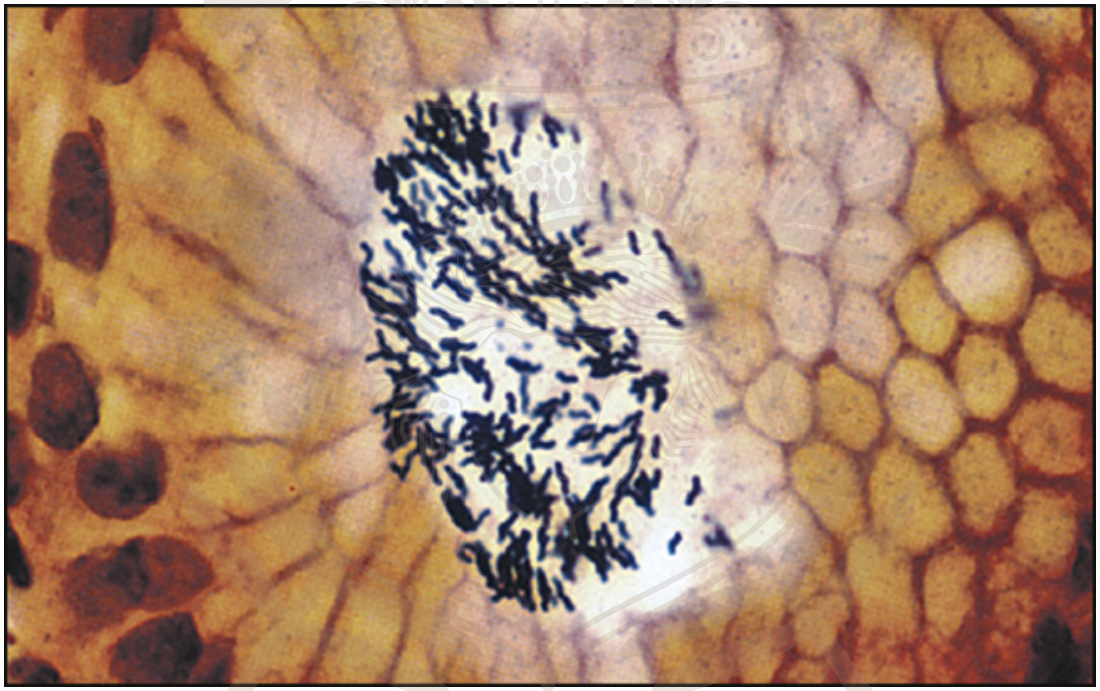

Figure 42.3 Helicobacter pylori in association with gastric mucosa.

B. H_2 receptor antagonists

Gastric acid secretion is stimulated by acetylcholine, histamine, and gastrin (Figure 42.4). The receptor-mediated binding of acetylcholine, histamine, or gastrin results in the activation of protein kinases, which in turn stimulates the H^+/K^+-adenosine triphosphatase (ATPase) proton pump to secrete hydrogen ions in exchange for K^+ into the lumen of the stomach. By competitively blocking the binding of histamine to H_2 receptors, *cimetidine* [si-MET-ih-deen], *famotidine*

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[fa-MOE-ti-deen], and *nizatidine* [nye-ZA-ti-deen] inhibit basal, food-stimulated, and nocturnal secretion of gastric acid, reducing acid secretion by approximately 70%. *Cimetidine* was the first H_2 receptor antagonist. However, its utility is limited by its adverse effect profile and drug–drug interactions. Another H_2 receptor antagonist *ranitidine* was removed from the market due to concerns of unsafe levels of N-Nitrosodimethylamine (NDMA), a potential human carcinogen, in *ranitidine* drug products.

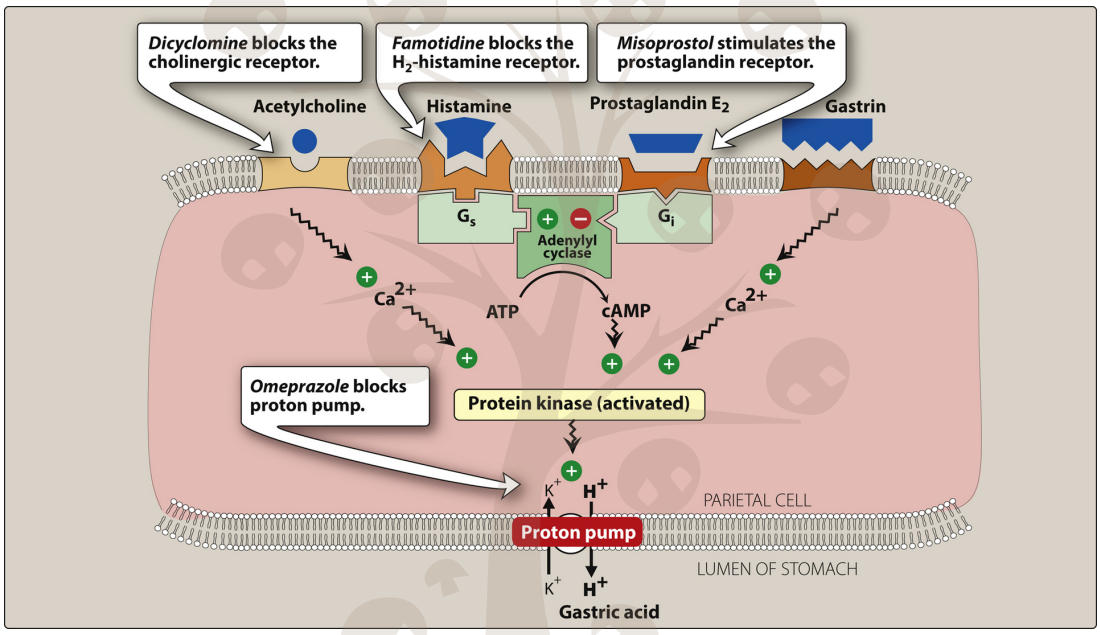

Figure 42.4 Effects of acetylcholine, histamine, prostaglandin E_2, and gastrin on gastric acid secretion by the parietal cells of stomach.G_s and G_i are membrane proteins that mediate the stimulatory or inhibitory effect of receptor coupling to adenylyl cyclase.

1.Actions: The histamine H_2 receptor antagonists act selectively on H_2 receptors in the stomach, without effects on H_1 receptors. They are competitive antagonists of histamine and are fully reversible.

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2. Therapeutic uses: H_2 receptor antagonists may be used in the treatment of peptic ulcer or management of heartburn. The use of these agents has decreased with the advent of PPIs.

a. Peptic ulcers: All H_2 receptor antagonists are equally effective in promoting the healing of duodenal and gastric ulcers. However, recurrence is common if H. pylori is present and the patient is treated with these agents alone. Patients with peptic ulcers related to H. pylori require antibiotics to eradicate the organism and prevent recurrence of the ulcer. Patients with NSAID-induced ulcers should be treated with PPIs, because these agents heal and prevent future ulcers more effectively than do H_2 receptor antagonists.

b. Acute stress ulcers: These drugs are given as an intravenous infusion to prevent and manage acute stress ulcers associated with high-risk patients in the intensive care setting. However, because tolerance may occur with these agents, PPIs are also used for this indication.

c. Gastroesophageal reflux disease: H_2 receptor antagonists are effective for the treatment of heartburn or GERD. H_2 receptor antagonists act by decreasing acid secretion; therefore, they may not relieve symptoms of heartburn for up to 45 minutes. Antacids more quickly and efficiently neutralize stomach acid, but their action is short lived. For these reasons, PPIs are now used preferentially in the treatment of GERD, especially for patients with severe and frequent heartburn.

3. Pharmacokinetics: After oral administration, the H_2 receptor antagonists distribute widely throughout the body (including into breast milk and across the placenta) and are excreted mainly in the urine. *Famotidine* is also available in an

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intravenous formulation. The half-life of these agents may be increased in patients with renal dysfunction, and dosage adjustments are needed.

4.Adverse effects: In general, the H_2 receptor antagonists are well tolerated. However, *cimetidine* can have endocrine effects, such as gynecomastia and galactorrhea (continuous release/discharge of milk), because it acts as a nonsteroidal antiandrogen. Other central nervous system effects such as confusion and altered mentation occur primarily in elderly patients and after intravenous administration. H_2 receptor antagonists may reduce the efficacy of drugs that require an acidic environment for absorption, such as *itraconazole. Cimetidine* inhibits several cytochrome P450 isoenzymes and can interfere with the metabolism of many drugs, such as *warfarin*, *phenytoin*, and *clopidogrel* (Figure 42.5).

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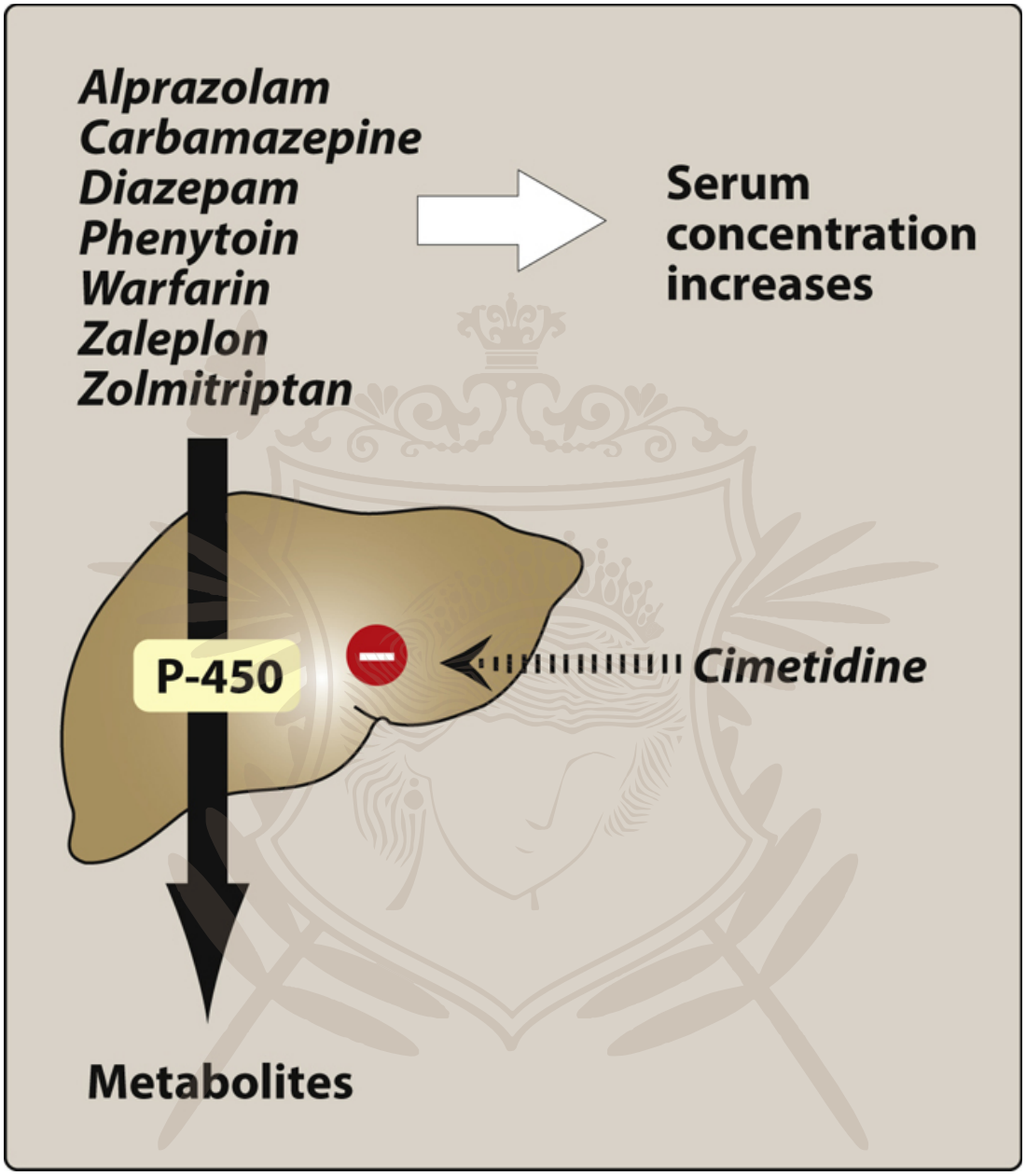

Figure 42.5 Drug interactions with *cimetidine*.

POLE STAR

C. Inhibitors of the H^+/K^+-ATPase proton pump

The PPIs bind to the H^+/K^+-ATPase enzyme system (proton pump) and suppress the secretion of hydrogen ions into the gastric lumen. The membrane-bound proton pump is the final step in the secretion of gastric acid (Figure 42.4). The available PPIs include *dexlansoprazole* [DEX-lan-SO-pra-zole], *esomeprazole* [es-oh-MEH-

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pra-zole], *lansoprazole* [lan-SO-pra-zole], *omeprazole* [oh-MEH-pra-zole], *pantoprazole* [pan-TOE-pra-zole], and *rabeprazole* [rah-BEH-pra-zole].

1.Actions: These agents are prodrugs with an acid-resistant enteric coating to protect them from premature degradation by gastric acid. The coating is removed in the alkaline duodenum, and the prodrug, a weak base, is absorbed and transported to the parietal cell. There, it is converted to the active drug and forms a stable covalent bond with the H^+/K^+-ATPase enzyme. It takes about 18 hours for the enzyme to be resynthesized, and acid secretion is inhibited during this time. At standard doses, PPIs inhibit both basal and stimulated gastric acid secretion by more than 90%. An oral product containing *omeprazole* combined with *sodium bicarbonate* for faster absorption is also available.

2.Therapeutic uses: The PPIs are superior to the H_2 antagonists in suppressing acid production and healing ulcers. Thus, they are the preferred drugs for the treatment of GERD, erosive esophagitis, active duodenal ulcer, and pathologic hypersecretory conditions such as Zollinger–Ellison syndrome. PPIs reduce the risk of bleeding from ulcers caused by *aspirin* and other NSAIDs and may be used for prevention or treatment of NSAID-induced ulcers. PPIs are also used for stress ulcer prophylaxis and management. Finally, PPIs are combined with antimicrobial regimens used to eradicate H. pylori.

3.Pharmacokinetics: These agents are effective orally. For maximum effect, PPIs should be taken 30–60 minutes before breakfast or the largest meal of the day. [Note: *Dexlansoprazole* has a dual delayed-release formulation and can be taken without regard to food.] *Esomeprazole* and *pantoprazole* are available in intravenous formulations. Although the plasma half-life of these agents is only a few hours, they have a long duration of action due to covalent

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bonding with the H^+/K^+-ATPase enzyme. Metabolites of these agents are excreted in urine and feces.

4.Adverse effects: The PPIs are generally well tolerated. PPIs may increase the risk of fractures, particularly if the duration of use is 1 year or greater (Figure 42.6). Prolonged acid suppression with PPIs (and H_2 receptor antagonists) may result in low vitamin B_{12} because acid is required for its absorption in a complex with intrinsic factor. Elevated gastric pH may also impair the absorption of *calcium carbonate. Calcium citrate* is an effective option for calcium supplementation in patients on acid suppressive therapy, since absorption of the citrate salt is not affected by gastric pH. Diarrhea and Clostridium difficile colitis may occur in patients receiving PPIs. Patients must be counseled to discontinue PPI therapy and contact their physician if they have diarrhea for several days. Additional adverse effects may include acute interstitial nephritis, hypomagnesemia, and an increased incidence of pneumonia.

POLE STAR

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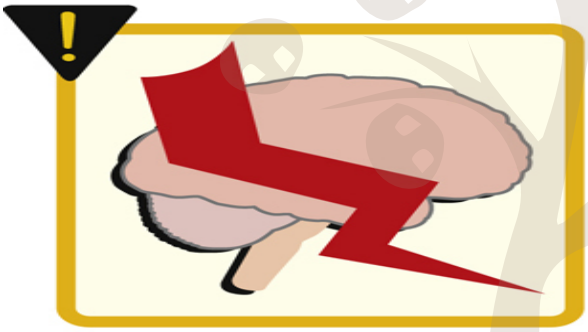
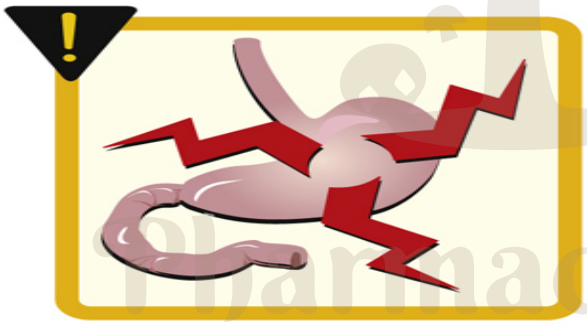
Nausea

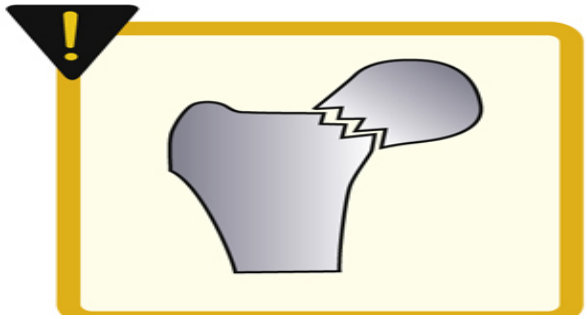
Diarrhea



Headache



GI disturbance



Bone Fractures
(increased risk
with long-term use:
hip, wrist, and spine)

Pharmacy Drug

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Figure 42.6 Some adverse effects of proton pump therapy.GI = gastrointestinal.

Clinical Application 42.1: Drug Interaction—Clopidogrel and Proton Pump Inhibitors

Clopidogrel is a prodrug that is metabolized to its active metabolite mainly via CYP2C19. Formation of the active metabolite is needed in order to produce the antiplatelet effect of *clopidogrel.* PPIs such as *omeprazole* and *esomeprazole* inhibit CYP2C19, resulting in significantly reduced antiplatelet activity of *clopidogrel.* Other PPIs (*dexlansoprazole*, *lansoprazole*, *pantoprazole*, and *rabeprazole*) do not affect CYP2C19 to this extent. *Clopidogrel* carries a boxed warning that concomitant use with *omeprazole* or *esomeprazole* should be avoided. Therefore, it is recommended that patients taking *clopidogrel* should be given an alternative PPI or an H_2 receptor antagonist.

D. Prostaglandins

Prostaglandin E, produced by the gastric mucosa, inhibits secretion of acid and stimulates secretion of mucus and bicarbonate (cytoprotective effect). A deficiency of prostaglandins is thought to be involved in the pathogenesis of peptic ulcers. *Misoprostol* [mye-soe-PROST-ole], an analog of prostaglandin E_1, is approved for the prevention of NSAID-induced gastric ulcers (Figure 42.7). Prophylactic use of *misoprostol* should be considered in patients who take NSAIDs and are at moderate to high risk of NSAID-induced ulcers, such as elderly patients and those with previous ulcers. *Misoprostol* is contraindicated in pregnancy, since it can stimulate uterine contractions and cause miscarriage. Dose-related diarrhea is the most common adverse effect and limits the use of this agent. Thus, PPIs are preferred agents for the prevention of NSAID-induced ulcers.

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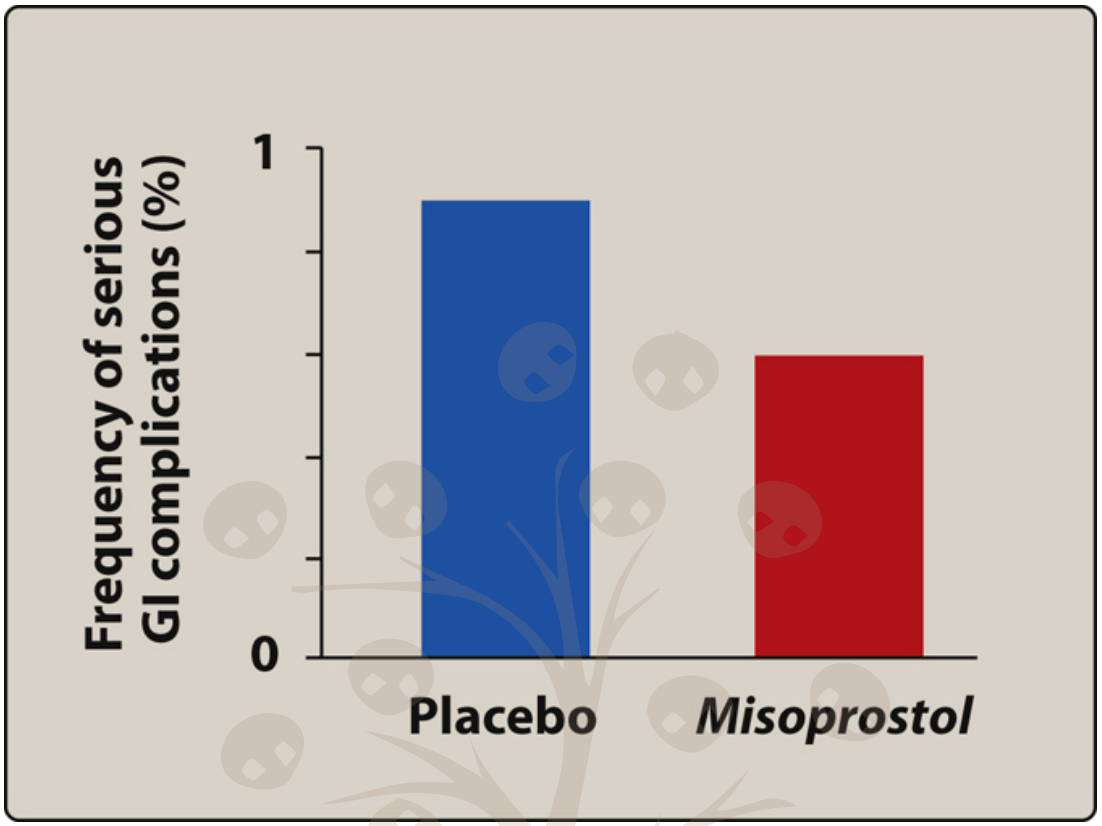

Figure 42.7 *Misoprostol* reduces serious gastrointestinal (GI) complications in patients with rheumatoid arthritis receiving NSAIDs. (Modified from F. E.Silverstein , D. Y.Graham , J. R.Senior . Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal antiinflammatory drugs. A randomized, double-blind, placebo controlled trial. *Ann. Intern. Med*. 123: 241 (1995).)

E. Antacids

Antacids are weak bases that react with gastric acid to form water and a salt to diminish gastric acidity. Because pepsin (a proteolytic enzyme) is inactive at a pH greater than 4, antacids also reduce pepsin activity.

1.Chemistry: Antacid products vary widely in their chemical composition, acid-neutralizing capacity, sodium content, and palatability. The efficacy of an antacid depends on its capacity to neutralize gastric HCl and on whether the stomach is full or

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empty. Food delays stomach emptying, allowing more time for the antacid to react and prolonging the duration of action. Commonly used antacids are combinations of salts of aluminum and magnesium, such as *aluminum hydroxide* and *magnesium hydroxide* [$Mg(OH)_2$]. *Calcium carbonate* [$CaCO_3$] reacts with HCl to form CO_2 and $CaCl_2$ and is also a commonly used preparation. Systemic absorption of *sodium bicarbonate* [$NaHCO_3$] can produce transient metabolic alkalosis and produce a significant sodium load. Therefore, this antacid is not recommended.

2.Therapeutic uses: Antacids are used for symptomatic relief of peptic ulcer disease, heartburn, and GERD. They should be administered after meals for maximum effectiveness. [Note: *Calcium carbonate* preparations are also used as calcium supplements for the prevention of osteoporosis.]

3.Adverse effects: *Aluminum hydroxide* tends to cause constipation, whereas *magnesium hydroxide* tends to produce diarrhea. Preparations that combine these agents aid in normalizing bowel function. Absorption of the cations from antacids (Mg^{2+}, Al^{3+}, Ca^{2+}) is usually not a problem in patients with normal renal function; however, accumulation and adverse effects may occur in patients with renal impairment.

F. Mucosal protective agents

Also known as cytoprotective compounds, these agents have several actions that enhance mucosal protection mechanisms, thereby preventing mucosal injury, reducing inflammation, and healing existing ulcers.

1.Sucralfate: This complex of *aluminum hydroxide* and sulfated sucrose binds to positively charged groups in proteins of both normal and necrotic mucosa. By forming complex gels with epithelial cells, *sucralfate* [soo-KRAL-fate] creates a

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physical barrier that protects the ulcer from pepsin and acid, allowing the ulcer to heal. Although *sucralfate* is effective for the treatment of duodenal ulcers and prevention of stress ulcers, its use is limited due to the need for multiple daily dosing, drug–drug interactions, and availability of more effective agents. Because it requires an acidic pH for activation, *sucralfate* should not be administered with PPIs, H_2 antagonists, or antacids. *Sucralfate* is well tolerated, but it can bind to other drugs and interfere with their absorption.

2. **Bismuth subsalicylate:** This agent is used as a component of quadruple therapy to heal H. pylori–related peptic ulcers. In addition to its antimicrobial actions, it inhibits the activity of pepsin, increases secretion of mucus, and interacts with glycoproteins in necrotic mucosal tissue to coat and protect the ulcer.

III. DRUGS USED TO CONTROL CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Although nausea and vomiting occur in a variety of conditions (for example, motion sickness, pregnancy, and GI illnesses) and are always unpleasant for the patient, the nausea and vomiting produced by chemotherapeutic agents demands especially effective management. Nearly 70%–80% of patients who undergo chemotherapy experience nausea and/or vomiting. Several factors influence the incidence and severity of chemotherapy-induced nausea and vomiting (CINV), including the specific chemotherapeutic drug (Figure 42.8); the dose, route, and schedule of administration; and patient variables. For example, young patients and women are more susceptible than older patients and men, and 10%–42% of patients experience nausea and/or vomiting in anticipation of chemotherapy (anticipatory vomiting). CINV not only

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affects quality of life but can also lead to rejection of potentially curative chemotherapy. In addition, uncontrolled vomiting can produce dehydration, profound metabolic imbalances, and nutrient depletion.

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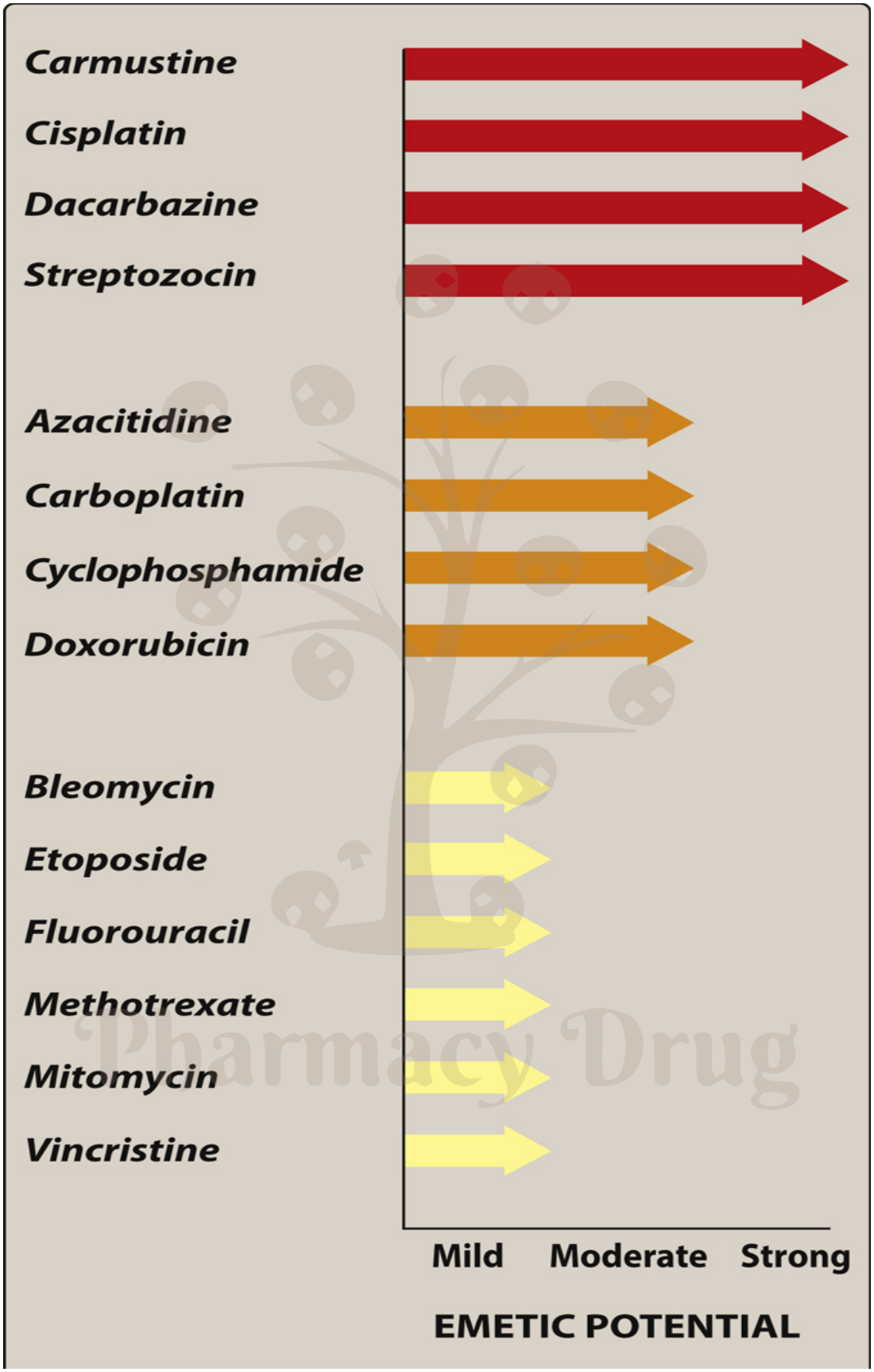

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Figure 42.8 Comparison of emetic potential of anticancer drugs.Data from S. M.Grunberg and P. J.Hesketh . Control of chemotherapy-induced emesis. *N. Engl. J. Med*. 329: 1790 (1993).

A. Mechanisms that trigger vomiting

Two brainstem sites have key roles in the vomiting reflex pathway. The chemoreceptor trigger zone (CTZ) is located in the area postrema (a circumventricular structure at the caudal end of the fourth ventricle). It is outside the blood–brain barrier. Thus, it can respond directly to chemical stimuli in the blood or cerebrospinal fluid. The second important site, the vomiting center, which is located in the lateral reticular formation of the medulla, coordinates the motor mechanisms of vomiting. The vomiting center also responds to afferent input from the vestibular system, the periphery (pharynx and GI tract), and higher brainstem and cortical structures. The vestibular system functions mainly in motion sickness.

B. Emetic actions of chemotherapeutic agents

Chemotherapeutic agents can directly activate the medullary CTZ or vomiting center. Several neuroreceptors, including dopamine receptor type 2 and serotonin type 3 (5-HT_3), play critical roles. Often, the color or smell of chemotherapeutic drugs (and even stimuli associated with chemotherapy) can activate higher brain centers and trigger emesis. Chemotherapeutic drugs can also act peripherally by causing cell damage in the GI tract and by releasing serotonin from the enterochromaffin cells of the small intestine. Serotonin activates 5-HT_3 receptors on vagal and splanchnic afferent fibers, which then carry sensory signals to the medulla, leading to the emetic response.

C. Antiemetic drugs

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Considering the complexity of the mechanisms involved in emesis, it is not surprising that antiemetics represent a variety of classes (Figure 42.9) and offer a range of efficacies (Figure 42.10). Anticholinergic drugs, especially the muscarinic receptor antagonist *scopolamine* and H_1-receptor antagonists, such as *dimenhydrinate*, *meclizine*, and *cyclizine*, are very useful in motion sickness but are ineffective against substances that act directly on the CTZ. The major categories of drugs used to control CINV include the following:

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PHENOTHIAZINES

Prochlorperazine GENERIC ONLY

5-HT_3 RECEPTOR ANTAGONISTS

Dolasetron ANZEMET
Granisetron SANCUSO, SUSTOL
Ondansetron ZOFRAN
Palonosetron ALOXI

SUBSTANCE P/NEUROKININ-1 RECEPTOR ANTAGONIST

Aprepitant, Fosaprepitant EMEND
*Netupitant, Fosnetupitant** AKYNZEO
Rolapitant VARUBI

CORTICOSTEROIDS

Dexamethasone DECADRON

SECOND-GENERATION ANTIPSYCHOTIC

Olanzapine ZYPREXA

SUBSTITUTED BENZAMIDES

Metoclopramide REGLAN

BUTYROPHENONES

Droperidol GENERIC ONLY
Haloperidol HALDOL

BENZODIAZEPINES

Alprazolam XANAX
Lorazepam ATIVAN

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Figure 42.9 Summary of drugs used to treat CINV.*In combination with *palonosetron*.

Pharmacy Drug

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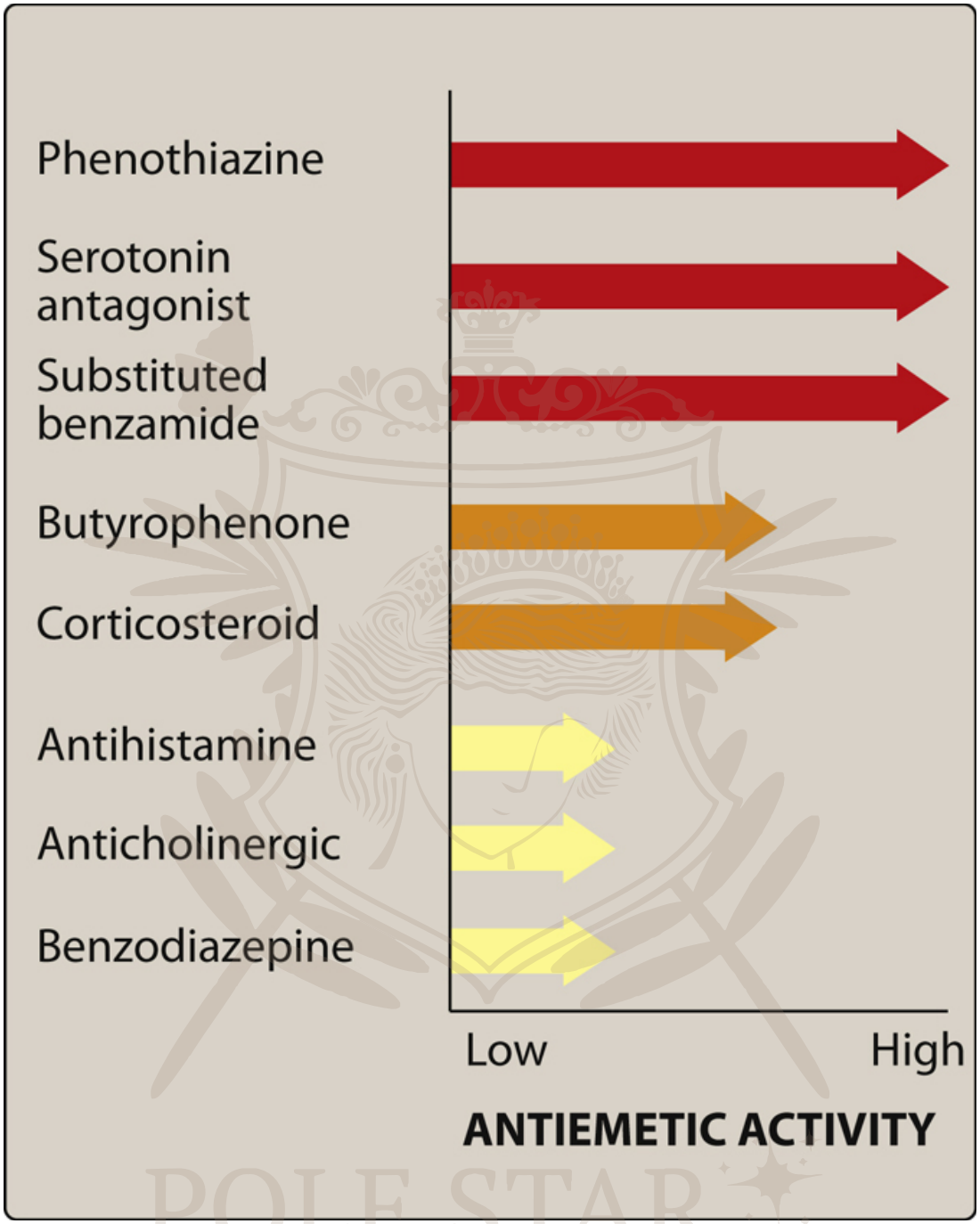

POLE STAR

Figure 42.10 Efficacy of antiemetic drugs.

1.Phenothiazines: Phenothiazines, such as *prochlorperazine* [proe-klor-PER-ah-zeen], act by blocking dopamine receptors in the CTZ. *Prochlorperazine* is effective in prophylaxis of CINV for chemotherapeutic agents with low

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emetogenic potential (for example, *fluorouracil* and *methotrexate*). Although increasing the dose improves antiemetic activity, adverse effects are dose limiting. The drug may also be used for the treatment of breakthrough CINV. [Note: Breakthrough CINV is nausea or vomiting that occurs despite the use of prophylactic antiemetics, and it requires immediate administration of additional antiemetics.]

2.5-HT$_3$ receptor antagonists: The 5-HT$_3$ receptor antagonists include *dolasetron* [dol-A-seh-tron], *granisetron* [gra-NI-seh-tron], *ondansetron* [on-DAN-seh-tron], and *palonosetron* [pa-low-NO-seh-tron]. These agents selectively block 5-HT$_3$ receptors in the periphery (visceral vagal afferent fibers) and in the CTZ. This class of agents is important in treating CINV, because of their superior efficacy and longer duration of action. These drugs can be administered as a single dose prior to chemotherapy (intravenously or orally) and are efficacious against all grades of emetogenic therapy. For multiday chemotherapy regimens, repeated dosing of 5-HT$_3$ receptor antagonists may be needed. [Note: *Palonosetron* has a much longer half-life than the other 5-HT$_3$ receptor antagonists (approximately 42 hours), and repeated dosing is generally not recommended.] *Ondansetron* and *granisetron* prevent emesis in 50%–60% of *cisplatin*-treated patients. These agents are also useful in the management of postoperative nausea and vomiting. 5-HT$_3$ antagonists are extensively metabolized by the liver; however, only *ondansetron* requires dosage adjustments in hepatic insufficiency. Excretion is via the urine. QT prolongation can occur with high doses of *ondansetron* and *dolasetron.* For this reason, the intravenous formulation of *dolasetron* was removed from the market, and the maximum dosage of *ondansetron* was limited.

3.Substance P/Neurokinin 1 receptor antagonists: *Aprepitant* [ah-PRE-pih-tant], *netupitant* [net-UE-pi-tant], and

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rolapitant [roe-LA-pi-tant] target the neurokinin receptor in the vomiting center and block the actions of substance P. [Note: *Fosaprepitant* and *fosnetupitant* are prodrugs of *aprepitant* and *netupitant*, respectively, that are administered intravenously.] These agents are indicated for highly or moderately emetogenic chemotherapy regimens, and they are usually administered with *dexamethasone* and a 5-HT_3 antagonist. Unlike most 5-HT_3 antagonists, these agents are effective for the delayed phase of CINV, which occurs 24 hours or more after chemotherapy. *Aprepitant* and *rolapitant* undergo hepatic metabolism, primarily by CYP3A4. Coadministration with strong inhibitors or inducers of CYP3A4 (for example, *clarithromycin* or *St. John's wort*, respectively) should be avoided. *Aprepitant* is an inducer of CYP3A4 and CYP2C9, and it also exhibits dose-dependent inhibition of CYP3A4. Therefore, it may affect the metabolism of other drugs that are substrates of these isoenzymes and is subject to numerous drug interactions. *Rolapitant* is a moderate inhibitor of CYP2D6. Fatigue, diarrhea, abdominal pain, and hiccups are adverse effects of this class.

4.Corticosteroids: *Dexamethasone* [dex-a-MEH-tha-sone] used alone is effective against mildly to moderately emetogenic chemotherapy. Most frequently, *dexamethasone* is used in combination with 5-HT_3 receptor antagonists or substance P/neurokinin 1 receptor antagonists for prevention of CINV in moderately or highly emetogenic chemotherapy regimens. The antiemetic mechanism is not known, but it may involve blockade of prostaglandins.

5.Second-generation antipsychotics: *Olanzapine* [oh-LANZ-ah-peen] is a second-generation antipsychotic (see Chapter 18) that blocks 5-HT_2 receptors and dopamine receptors, in addition to histamine-1 and α_1 receptors. It is useful in the prevention of CINV and is used in combination

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with 5-HT_3 receptor antagonists and *dexamethasone* (with or without substance P/neurokinin 1 receptor antagonists) for moderately or highly emetogenic chemotherapy regimens.

6.Substituted benzamides: One of several substituted benzamides with antiemetic activity, *metoclopramide* [met-oh-kloe-PRAH-mide] is effective at high doses against the emetogenic *cisplatin*, preventing emesis in 30%–42% of patients and reducing emesis in the majority of patients. *Metoclopramide* accomplishes this through inhibition of dopamine in the CTZ. Because it is less effective than other agents, *metoclopramide* should be reserved for patients who have inadequate response to 5-HT_3 receptor antagonists or substance P/neurokinin 1 receptor antagonists. It is effective in the management of breakthrough nausea and vomiting. *Metoclopramide* enhances gastric motility and is useful for patients with gastroparesis. Antidopaminergic adverse effects, including extrapyramidal symptoms, limit long-term high-dose use. The agent carries a boxed warning against use for more than 12 weeks due to the risk of tardive dyskinesia.

7.Butyrophenones: *Droperidol* [droe-PER-i-doll] and *haloperidol* [hal-oh-PER-i-doll] act by blocking dopamine receptors. The butyrophenones are moderately effective antiemetics. *Haloperidol* is used in the management of breakthrough CINV. *Droperidol* may prolong the QT_c interval, and use should be reserved for patients with nausea and vomiting related to surgical procedures and inadequate response to other agents.

8.Benzodiazepines: The antiemetic potency of *lorazepam* [lor-A-ze-pam] and *alprazolam* [al-PRAH-zoe-lam] is low. Their beneficial effects may be due to their sedative, anxiolytic, and amnestic properties (see Chapter 16). These properties make benzodiazepines useful in treating anticipatory vomiting.

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Concomitant use of alcohol should be avoided due to additive CNS depressant effects.

IV. ANTIDIARRHEALS

Increased motility of the GI tract and decreased absorption of fluid are major factors in diarrhea. Antidiarrheal drugs include antimotility agents, adsorbents, and drugs that modify fluid and electrolyte transport (Figure 42.11).

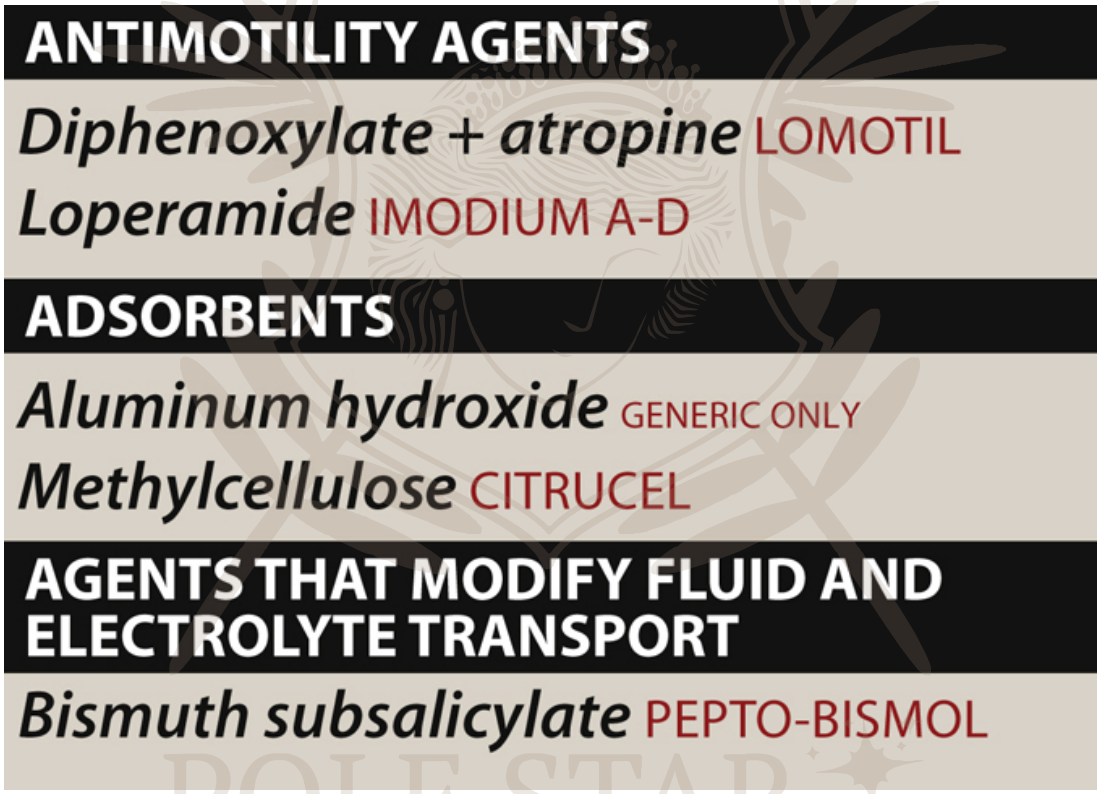

Figure 42.11 Summary of drugs used to treat diarrhea.

A. Antimotility agents

Two drugs used to control diarrhea are *diphenoxylate* [dye-fen-OKS-i-late] and *loperamide* [loe-PER-ah-mide]. Both are analogs of *meperidine* and have opioid-like actions on the gut. They

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activate presynaptic opioid receptors in the enteric nervous system to inhibit acetylcholine release and decrease peristalsis. At the usual doses, they lack analgesic effects. *Loperamide* is more widely used for the general treatment of acute diarrhea, including traveler's diarrhea. It is available without a prescription in many countries. Misuse or overuse of high doses of *loperamide* has been observed in patients attempting to obtain euphoria or prevent withdrawal from opioids. As a result, limited quantities of *loperamide* can be sold at one time, and the agent carries a boxed warning regarding the importance of following recommended dosage instructions to avoid severe adverse reactions. Because these drugs can contribute to toxic megacolon, they should not be used in patients with active ulcerative colitis. In addition, these agents should be avoided in young children due to the risk of respiratory depression, cardiac events, coma, and death. Patients with potentially severe infectious diarrhea (for example, fever or blood or mucus in the stool) should avoid self-treatment with *loperamide*, as the antimotility effect may prevent expulsion of the causative pathogen and prolong the duration of illness.

B. Adsorbents

Adsorbent agents, such as *aluminum hydroxide* and *methylcellulose* [METH-il-SEL-yoo-los], are used to control diarrhea. Presumably, these agents act by adsorbing intestinal toxins or microorganisms and/or by coating or protecting the intestinal mucosa. They are much less effective than antimotility agents, and they can interfere with the absorption of other drugs.

C. Agents that modify fluid and electrolyte transport

Bismuth subsalicylate, used for prevention and treatment of traveler's diarrhea, decreases fluid secretion in the bowel. Its action may be due to its salicylate component as well as its coating action. Adverse effects may include black tongue and black stools.

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V. LAXATIVES

Laxatives are commonly used in the treatment of constipation to accelerate the motility of the bowel, soften the stool, and increase the frequency of bowel movements. These drugs are classified on the basis of their mechanism of action (Figure 42.12). Laxatives increase the potential for loss of pharmacologic effect of poorly absorbed, delayed-acting, and extended-release oral preparations of other medications by accelerating their transit through the intestines. They may also cause electrolyte imbalances when used chronically. Many of these drugs have a risk of dependency for the user.

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Figure 42.12 Summary of drugs used to treat constipation.

A. Irritants and stimulants

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1. **Senna:** This agent is a widely used stimulant laxative. Its active ingredient is a group of sennosides, a natural complex of anthraquinone glycosides. Taken orally, *senna* causes evacuation of the bowels within 6 to 12 hours. It also causes water and electrolyte secretion into the bowel. In combination products with a *docusate*-containing stool softener, it is useful in treating opioid-induced constipation.

2. **Bisacodyl:** Available as suppositories and enteric-coated tablets, *bisacodyl* [bis-ak-oh-dil] is a potent stimulant of the colon. It acts directly on nerve fibers in the mucosa of the colon.

3. **Castor oil:** This agent is broken down in the small intestine to ricinoleic acid, which is very irritating to the stomach and promptly increases peristalsis. Pregnant patients should avoid *castor oil* because it may stimulate uterine contractions. Use of *castor oil* is generally not recommended due to poor palatability and potential for GI adverse effects.

B. Bulk laxatives

The bulk laxatives include hydrophilic colloids (from indigestible parts of fruits and vegetables). They form gels in the large intestine, causing water retention and intestinal distension, thereby increasing peristaltic activity. Similar actions are produced by *methylcellulose*, psyllium seeds, and bran. They should be used cautiously in patients who are immobile because of their potential for causing intestinal obstruction. *Psyllium* can reduce the absorption of other oral drugs, and administration of other agents should be separated from *psyllium* by at least 2 hours.

C. Saline and osmotic laxatives

Saline cathartics, such as *magnesium citrate* and *magnesium hydroxide*, are nonabsorbable salts (anions and cations) that hold water in the intestine by osmosis. This distends the bowel, increasing intestinal activity and producing defecation in a few

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hours. Electrolyte solutions containing *polyethylene glycol* (*PEG*) are used as colonic lavage solutions to prepare the gut for radiologic or endoscopic procedures. *PEG* powder for solution without electrolytes is also used as a laxative and has been shown to cause less cramping and gas than other laxatives. *Lactulose* is a semisynthetic disaccharide sugar that acts as an osmotic laxative. It cannot be hydrolyzed by GI enzymes. Oral doses reach the colon and are degraded by colonic bacteria into lactic, formic, and acetic acids. This increases osmotic pressure, causing fluid accumulation, colon distension, soft stools, and defecation. [Note: *Lactulose* is also used for the treatment of hepatic encephalopathy, due to its ability to reduce ammonia levels.]

D. Stool softeners (emollient laxatives or surfactants)

Surface active agents that become emulsified with the stool produce softer feces and ease passage of stool. These include *docusate sodium* and *docusate calcium.* They may take days to become effective and are often used for prophylaxis rather than acute treatment. Stool softeners should not be taken concomitantly with *mineral oil* because of the potential for absorption of the *mineral oil*.

E. Lubricant laxatives

Mineral oil and *glycerin* suppositories are lubricants and act by facilitating the passage of hard stools. *Mineral oil* should be taken orally in an upright position to avoid its aspiration and potential for lipid or lipoid pneumonia.

F. Chloride channel activators

Lubiprostone [loo-bee-PROS-tone] works by activating chloride channels to increase fluid secretion in the intestinal lumen. This eases the passage of stools and causes little change in electrolyte balance. *Lubiprostone* is used in the treatment of chronic constipation and irritable bowel syndrome with constipation (IBS-C), particularly because tolerance or dependency has not been

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associated with this drug. Also, drug–drug interactions are minimal because metabolism occurs quickly in the stomach and jejunum.

VI. IRRITABLE BOWEL SYNDROME

IBS is characterized by chronic abdominal pain and altered bowel habits in the absence of an organic cause. IBS may be classified as constipation predominant (IBS-C), diarrhea predominant (IBS-D), or a combination of both. Diet and psychosocial modifications play an important role in management of the disease, as well as drug therapy (Figure 42.13). Key characteristics of medications used for the treatment of IBS-C and IBS-D are provided in Figure 42.14.

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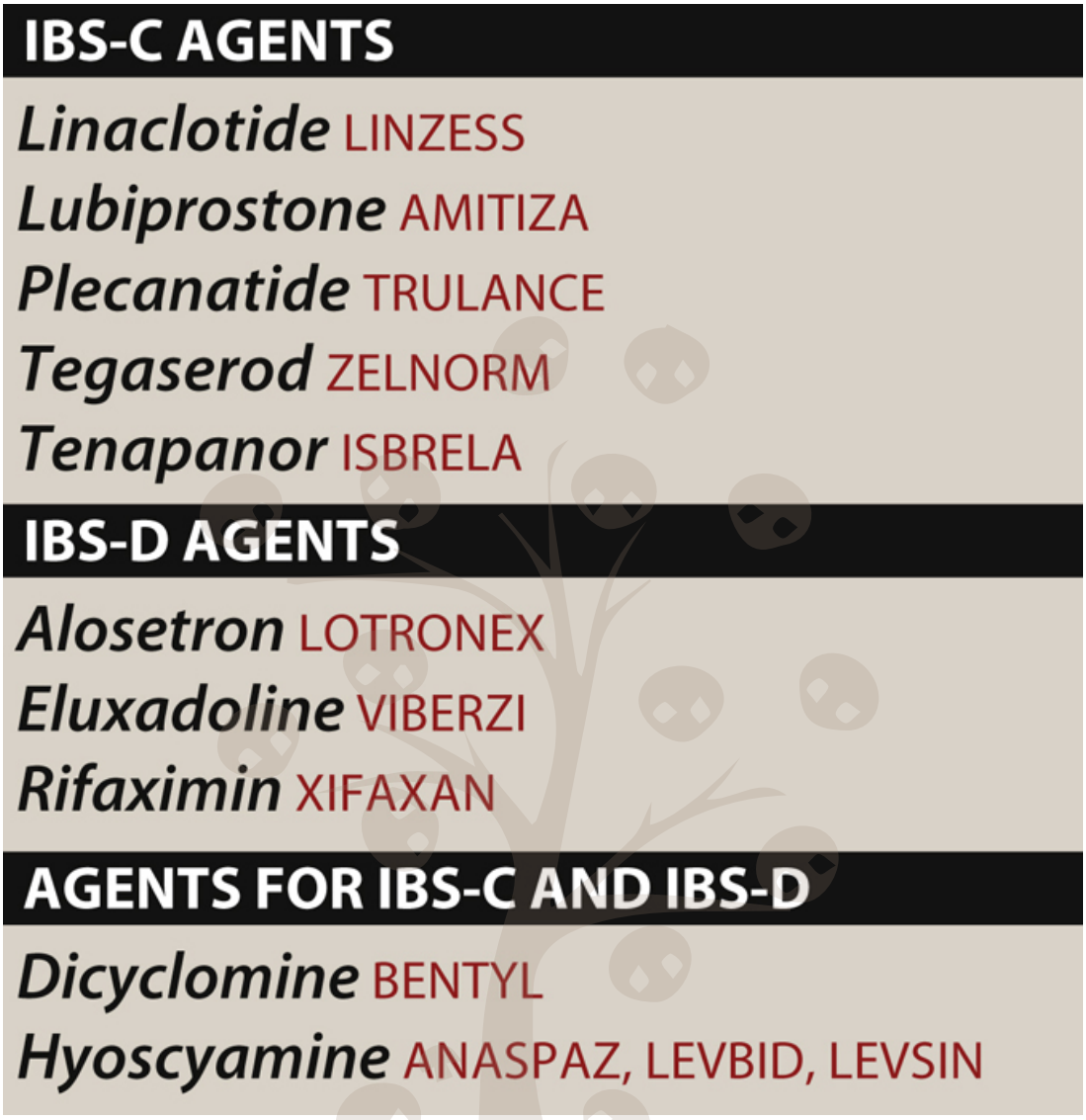

Figure 42.13 Summary of drugs used to treat irritable bowel syndrome.IBS-C = irritable bowel syndrome with constipation; IBS-D = irritable bowel syndrome with diarrhea.

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DRUG	INDICATION	MECHANISM OF ACTION	ADVERSE EFFECTS
Linaclotide *Plecanatide*	IBS-C*	Guanylate cyclase-C agonist	Diarrhea Do not use in GI obstruction
Lubiprostone	Women with IBS-C*^	Chloride channel activator	Nausea and vomiting, diarrhea Do not use in GI obstruction
Tegaserod	Women with IBS-C and < 65 years old	5-HT_4 partial agonist	Diarrhea Do not use in GI obstruction or history of MI, stroke, or angina
Tenapanor	IBS-C	Sodium/hydrogen exchanger 3 (NHE3) inhibitor	Diarrhea Do not use in GI obstruction
Alosetron	Women with severe IBS-D	5-HT_3 antagonist	Constipation, nausea and vomiting, heartburn, ischemic colitis (rare)
Eluxadoline	IBS-D	μ-Opioid receptor agonist	Constipation, abdominal pain, nausea, pancreatitis (rare) Avoid use in pancreatitis or alcoholism
Rifaximin	Short-term use in IBS-D	Decreases bacterial load (structural analog of *rifampin*)	Nausea, fatigue, headache, dizziness, peripheral edema, and risk of Clostridium difficile infection
Dicyclomine	IBS-C and IBS-D	Antimuscarinic; decreases GI spasms and motility	Anticholinergic effects such as drowsiness and dry mouth
Hyoscyamine	IBS-C and IBS-D	Antimuscarinic; decreases GI spasms and motility	Anticholinergic effects such as drowsiness and dry mouth Overdose may produce hallucinations, arrhythmias, and nausea and vomiting

Figure 42.14 Characteristics of drugs used to treat irritable bowel syndrome in adults.IBS-C = irritable bowel syndrome with constipation; IBS-D = irritable bowel syndrome with diarrhea; GI = gastrointestinal; MI = myocardial infarction *Also indicated for the treatment of chronic idiopathic constipation. ^Also indicated for the treatment of opiate-induced constipation.

VII. DRUGS USED TO TREAT INFLAMMATORY BOWEL DISEASE

IBD is a group of idiopathic chronic intestinal conditions characterized by immune-mediated GI tract inflammation in response to bacterial antigens in the intestinal lumen. The most common subtypes of IBD are Crohn disease (CD) and ulcerative colitis (UC). CD can affect any portion of the GI tract from the mouth to the anus in a noncontinuous fashion and is characterized by transmural inflammation. UC usually affects the rectum. It may extend continuously to affect other parts of the colon and is

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characterized by inflammation limited to the mucosal layer (Figure 42.15). Severity, extent of disease, and risk of complications guide treatment of IBD. Remission of IBD can be induced with the use of rectal and oral 5-aminosalicylates (5-ASAs), corticosteroids (rectal, oral locally delivered, and systemic), biologic agents (TNF-α inhibitors, α-4 integrin inhibitors, and the IL-12/23 inhibitor *ustekinumab*), and the Janus kinase inhibitor, *tofacitinib.* Drugs used to maintain remission are the same as those used for induction. The immunomodulators (*azathioprine*, *6-mercaptopurine*, and *methotrexate*) are additional agents used in the maintenance of remission in IBD. Figure 42.16 summarizes agents used in the treatment of IBD.

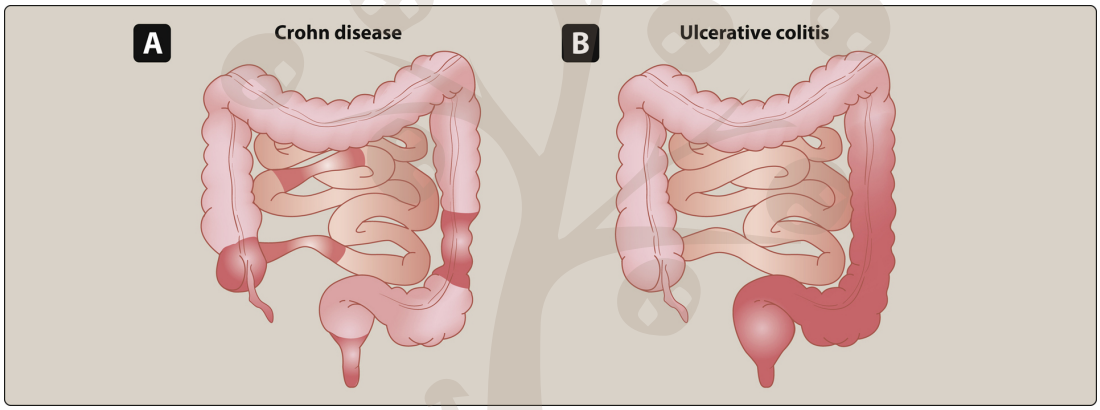

Figure 42.15 Distribution patterns of disease with **(A)** skip lesions in Crohn disease and **(B)** continuous involvement of the colon, beginning with the rectum, in ulcerative colitis.

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5-AMINOSALICYLATES

Oral Formulation

- *Balsalazide* COLAZAL
- *Mesalamine* ASACOL HD, PENTASA
- *Olsalazine* DIPENTUM
- *Sulfasalazine* AZULFIDINE

Rectal Formulation

- *Mesalamine enema* ROWASA
- *Mesalamine suppository* CANASA

CORTICOSTEROIDS

Oral Formulation

- *Budesonide delayed-release* ENTOCORT EC
- *Budesonide extended-release* UCERIS
- *Hydrocortisone* CORTEF
- *Prednisone* DELTASONE
- *Methylprednisolone* MEDROL

Intravenous Formulation

- *Hydrocortisone* SOLU-CORTEF
- *Methylprednisolone* SOLU-MEDROL

Rectal Formulation

- *Budesonide foam* UCERIS RECTAL
- *Hydrocortisone suppository* ANUCORT-HC
- *Hydrocortisone enema* CORTENEMA
- *Hydrocortisone foam* CORTIFOAM

BIOLOGIC AGENTS

TNF-α Inhibitors

- *Adalimumab* HUMIRA
- *Certolizumab* CIMZIA
- *Golimumab* SIMPONI
- *Infliximab* REMICADE

α4-Integrin Inhibitors

- *Vedolizumab* ENTYVIO

IL-12/23 Inhibitor

- *Ustekinumab* STELARA

JANUS KINASE INHIBITORS

Tofacitinib XELJANZ

IMMUNOMODULATORS

Azathioprine IMURAN
6-Mercaptopurine GENERIC ONLY
Methotrexate VARIOUS

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Figure 42.16 Agents used in the treatment of IBD.

A. 5-Aminosalicylates

The 5-ASA agents include *sulfasalazine* [SUL-fa-SAL-a-zeen], *mesalamine* [me-SAL-a-meen], *balsalazide* [bal-SAL-a-zide], and *olsalazine* [ole-SAL-a-zeen]. [Note: *mesalamine* is 5-ASA.] The first 5-ASA agent used in the treatment of IBD, *sulfasalazine*, is a prodrug consisting of 5-ASA linked to sulfapyridine. Colonic bacteria cleave *sulfasalazine* to produce 5-ASA (*mesalamine*) and sulfapyridine (Figure 42.17). When it became known that 5-ASA was responsible for the efficacy of *sulfasalazine* while sulfapyridine was mainly responsible for its adverse effects, unlinked 5-ASA formulations were produced. However, unlinked 5-ASA is rapidly absorbed, with only 20% reaching the site of action in the terminal ileum and colon. Therefore, other azo bonded compounds and various formulations of *mesalamine* were developed to limit absorption of 5-ASA in the proximal GI tract and allow increased drug delivery to the colon. The oral *mesalamine* compounds consist of single 5-ASA molecules enclosed within an enteric coat or a semipermeable membrane, which provides for delayed or extended release of the drug. The azo compounds (*balsalazide* and *olsalazine*) are prodrugs that consist of a 5-ASA molecule bound via an azo (N=N) bond to another molecule. These formulations differ in their sites of topical delivery within the intestinal tract and dosing frequency (Figure 42.18). Compared with *sulfasalazine*, the *mesalamine* formulations and the other azo compounds have improved tolerability with similar efficacy, making them the mainstay of therapy in UC.

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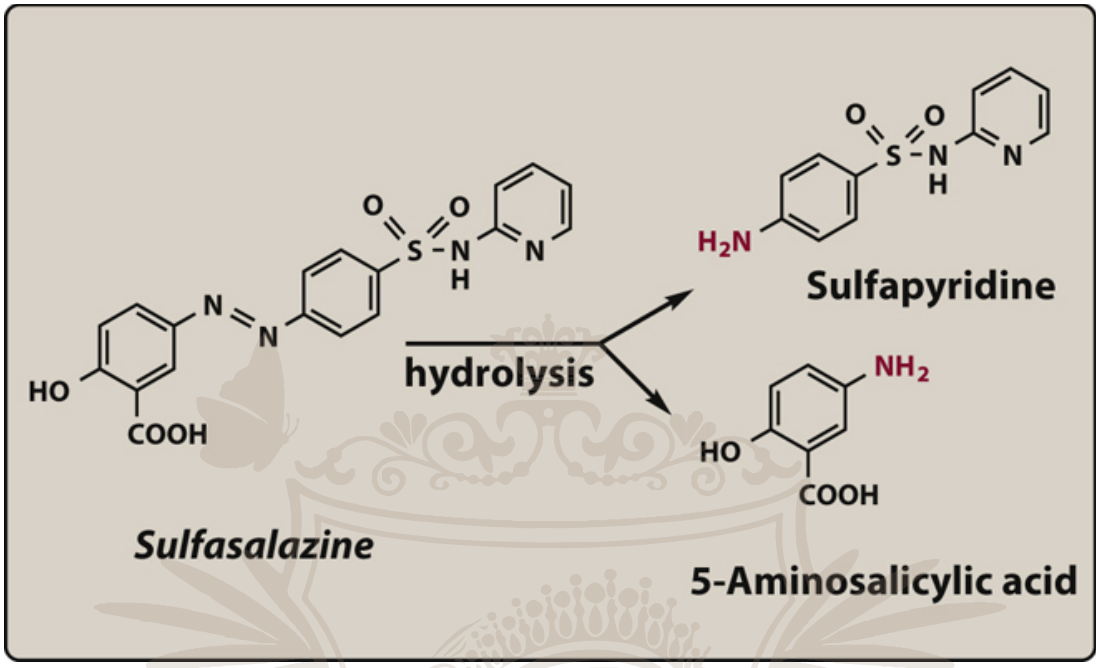

Figure 42.17 *Sulfasalazine* metabolism.

DRUG	BRAND(S)	ROUTE	DOSING FREQUENCY	FORMULATION	SITE OF DELIVERY
Balsalazide	Colazal	PO	Three times daily	5-ASA azo bonded to inert carrier molecule; release dependent on cleavage by colonic bacteria	Colon
Mesalamine	Apriso	PO	Once daily	pH-dependent (≥ 6) delayed release with extended-release matrix core	Colon
	Asacol HD	PO	Three times daily	pH-dependent (≥ 7) delayed release	Distal ileum, colon
	Canasa	Rectal	Once daily	Suppository	Rectum
	Lialda	PO	Once daily	pH-dependent (≥ 7) delayed-release multimatrix system	Distal ileum, colon
	Pentasa	PO	Four times daily	Ethyl cellulose membrane controlled-release micropellets	Entire small intestine, colon
	Rowasa	Rectal	Once daily	Liquid enema	Rectum, sigmoid colon
Olsalazine	Dipentum	PO	Twice daily	5-ASA azo bonded to another 5-ASA molecule; release dependent on cleavage by colonic bacteria	Colon

Figure 42.18 5-Aminosalicylate formulations.

1.Actions: The 5-ASAs exhibit anti-inflammatory and immunosuppressive properties that are the main determinants of their efficacy in IBD. The exact mechanism of action of 5-

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ASA is unknown but is thought to be due in part to (1) inhibition of cytokine and prostaglandin synthesis; (2) inhibition of leukotriene release; (3) scavenging of free radicals; (4) inhibition of T-cell proliferation, activation, and differentiation; and (5) impairment of leukocyte adhesion and function. 5-ASA is thought to act via topical interaction with the intestinal mucosa, and the mechanisms are the same with both oral and rectal administration.

2.Therapeutic uses: The 5-ASA drugs are the mainstay of treatment in UC. All 5-ASA formulations and *sulfasalazine* are indicated in UC for induction and maintenance of remission. Current guidelines recommend *mesalamine*, *balsalazide*, or *olsalazine* as first line for mild–moderate disease. Patients with moderate–severe UC may require use of biologic agents and immunomodulators. Use of 5-ASA drugs in CD is limited due to a general lack of efficacy.

3.Pharmacokinetics: 5-ASA (*mesalamine*) pharmacokinetics are variable and dependent on route of administration (for example, rectal vs. oral), type of oral formulation (see Figure 42.18), and disease activity. Absorption of 5-ASA increases with more severe disease and decreases with decreasing pH. In UC, 5-ASAs work by local effect. Therefore, the 5-ASA preparations deliver drug to the colon for maximal intestinal exposure. Absorption of rectally administered *mesalamine* and systemic exposure depends on rectal retention time. Due to the topical mechanism of action, differences in systemic exposure are not related to efficacy but may be important for adverse effects. *Sulfasalazine* is administered orally, with the sulfapyridine component having significant absorption (60%–80%).

4.Adverse effects: Adverse effects of *sulfasalazine* occur in up to 45% of patients, with the majority due to the sulfapyridine component. Headache, nausea, and fatigue are most common and are dose related. Serious reactions include

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hemolytic anemia, myelosuppression, hepatitis, pneumonitis, nephrotoxicity, fever, rash, and Stevens–Johnson syndrome. Treatment should be discontinued at the first sign of skin rash or hypersensitivity. *Sulfasalazine* reversibly impairs male fertility. *Sulfasalazine* also inhibits intestinal folate absorption, and folate supplementation is recommended with chronic use. The newer *mesalamine* formulations are well tolerated; headache and dyspepsia are the most common adverse effects. Rarely, acute interstitial nephritis may occur and renal function should be monitored in patients receiving *mesalamine.* Watery diarrhea occurs in up to 20% of patients treated with *olsalazine.* Some formulations of *mesalamine* depend on pH for their release (see Figure 42.18), and coadministration of drugs that increase pH (for example, PPIs, H_2 receptor antagonists, and antacids) may result in increased systemic absorption and premature release of 5-ASA before reaching the site of action. Concomitant use should be avoided or another formulation of 5-ASA that is non–pH dependent should be used (for example, *olsalazine*, *balsalazide*).

B. Corticosteroids

Corticosteroids are used in IBD for their anti-inflammatory effects as they are in other inflammatory conditions (see Chapter 26). Although corticosteroids are very effective at inducing remission in IBD, long-term maintenance with corticosteroids should be avoided due to the deleterious effects of chronic use. Rectal formulations (for example, *hydrocortisone* enema and *budesonide* foam) have fewer adverse effects than systemic steroids, but use is limited to left-sided disease in UC. Enteric-release preparations of oral *budesonide* deliver corticosteroid to a portion of inflamed intestine. This agent has minimal systemic adverse effects due to low bioavailability resulting from extensive first-pass hepatic metabolism. Delayed-release *budesonide* delivers drug to the terminal ileum and proximal large bowel and is used in ileocecal

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CD. Extended-release *budesonide* delivers drug throughout the colon and is used in UC patients with pancolitis. Although systemic exposure is less than other corticosteroids, the use of *budesonide* in extended maintenance of remission is limited due to concerns with long-term use.

C. Biologic agents

The TNF-α inhibitors, α-4 integrin inhibitors, and the IL-12/23 inhibitor *ustekinumab* are biologic agents used in the management of IBD. Use of these agents is associated with an increased risk for infection. Patients should be evaluated for tuberculosis, and treatment for latent TB should be considered prior to use of these drugs. Many of these agents have other therapeutic indications such as rheumatoid arthritis (see Chapter 40) or psoriasis (see Chapter 45). The actions, pharmacokinetics, and adverse effects of these drugs in other conditions are similar in IBD.

1. TNF-α inhibitors: TNF-α inhibitors are parenteral monoclonal antibodies that are effective for both induction and maintenance of remission in IBD. *Infliximab* [in-FLIX-ih-mab] and *adalimumab* [AY-da-LIM-ue-mab] are indicated in both moderate–severe CD and UC. *Certolizumab* [SER-toe-LIZ-oo-mab] is indicated for moderate–severe CD, and *golimumab* [goe-LIM-ue-mab] is indicated for moderate–severe UC. The TNF-α inhibitors are generally reserved as second-line agents in patients with UC who have failed 5-ASAs, are unresponsive to or dependent on corticosteroids, or who present with more severe disease. In CD, the TNF-α inhibitors have a first-line role in patients with moderate–severe disease and those at higher risk of progression and worse outcomes. These agents are associated with the development of immunogenicity and antidrug antibodies that can result in loss of response in a significant proportion of patients.

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Clinical Application 42.2: Therapeutic Drug Monitoring for Biologic Agents

Biologic drugs (for example, TNF-α inhibitors) are associated with the development of immunogenicity and antidrug antibodies that can result in loss of response in a significant proportion of patients with IBD. Serum levels of biologic drugs and their associated antidrug antibodies can be measured. Therefore, it is recommended that patients with a loss of response to a specific biologic drug have therapeutic drug monitoring (TDM) performed to measure serum trough levels of both the specific biologic drug and its associated antidrug antibodies. TDM can guide the clinician in adjusting dose or dosing interval or in changing therapy to another agent to improve response in patients with IBD.

2.α-4 integrin inhibitors: α-4 Integrins are adhesion molecules that promote leukocyte migration to sites of inflammation. Use of α-4 integrin inhibitors reduces lymphocyte migration into the intestinal mucosa and inflammation. *Vedolizumab* [VE-doe-LIZ-ue-mab] is a humanized monoclonal antibody that exhibits specific binding to α-4/β-7 integrin and is indicated in moderate–severe UC and CD for induction of remission and maintenance. The most common adverse reactions include headache, arthralgia, nausea, fatigue, and musculoskeletal pain.

3.IL-12/23 inhibitor: *Ustekinumab* [YOO-sti-KIN-ue-mab] inhibits the cytokines IL-12 and IL-23 involved in lymphocyte activation. It is indicated for psoriasis, psoriatic arthritis, and induction and maintenance of remission in CD in patients refractory to or intolerant of TNF-α inhibitors, immunomodulators, or corticosteroids. Common adverse effects include headache, arthralgia, infection, nausea, and nasopharyngitis.

D. Janus kinase inhibitors

The Janus kinase (JAK) inhibitors are used for rheumatoid arthritis, psoriasis, and other conditions (see Chapters 40 and 45) and function by inhibiting one or more of the Janus kinase family

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of enzymes (JAK1, JAK2, JAK3). *Tofacitinib* [toe-fa-SYE-ti-nib], a JAK1/JAK3 inhibitor, is indicated for treatment of moderate–severe UC. The mechanism of action of *tofacitinib* involves interference with the JAK-STAT signaling pathway resulting in decreased proliferation and differentiation of macrophage and T cells. *Tofacitinib* is currently recommended as monotherapy in moderate–severe UC in patients who are refractory to or intolerant of TNF-α inhibitors. *Tofacitinib* can be used for induction and maintenance of remission and has the advantage of oral administration. As with the use of biologic drugs, *tofacitinib* is associated with increased risk for infection, including a specific increased risk of herpes zoster infection. Patients should be evaluated for herpes zoster immunization prior to beginning therapy with *tofacitinib.* Common side effects include nasopharyngitis, arthralgia, and headache.

E. Immunomodulators

The immunomodulator drugs most often used in IBD are *methotrexate* and the thiopurines *azathioprine* and *6-mercaptopurine* (*6-MP*). *Methotrexate* (*MTX*) also has therapeutic applications in cancer, rheumatoid arthritis, and psoriasis (see Chapters 37, 40, and 45). The actions, pharmacokinetics, and adverse effects of the immunomodulators in other conditions are similar in IBD.

1.Methotrexate: *MTX* is a structural analogue of folic acid that inhibits the production of folinic acid. The exact mechanism of action in CD is unknown. Only intramuscular or subcutaneous administration of *MTX* has efficacy in CD. *MTX* is a recommended monotherapy option for maintenance of remission in CD but is not recommended in maintenance for UC. Common adverse effects of *MTX* are headache, nausea, vomiting, abdominal discomfort, serum aminotransferase elevations, and rash. Administration of folic acid is effective at reducing the incidence of GI adverse effects and is recommended in patients receiving *MTX*.

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2.Thiopurines: The thiopurines *azathioprine* and *6-mercaptopurine* (*6-MP*) are oral medications that have corticosteroid-sparing effects in patients with UC and CD. They are considered first line as monotherapy for maintenance of remission. Use of thiopurines in IBD is limited by concerns of toxicity, including bone marrow suppression and hepatotoxicity. Monitoring of complete blood counts and liver function tests is recommended in all patients treated with a thiopurine.

Chapter Summary:

- Peptic ulcer disease (PUD) is most commonly caused by the bacteria H. pylori or the use of NSAIDs. It is treated with antimicrobial agents to eradicate the infection when H. pylori is present. Quadruple therapy of *bismuth subsalicylate*, *metronidazole*, and *tetracycline* plus a proton pump inhibitor is a recommended first-line option for PUD secondary to H. pylori infection.
- Proton pump inhibitors (PPIs; for example, *omeprazole*) bind to the H^+/K^+-ATPase enzyme system (proton pump) and suppress the secretion of hydrogen ions into the gastric lumen.
- By competitively blocking the binding of histamine to H_2 receptors, H_2 receptor antagonists (for example, *famotidine*) inhibit gastric acid secretion.
- H_2 receptor antagonists are less effective than PPIs in the treatment of PUD and severe heartburn.
- Long-term usage of PPIs has been associated with an increased risk of fracture, low vitamin B_{12} levels, Clostridium difficile infection, and acute interstitial nephritis.
- Antacids work by neutralizing gastric acid and are used for short-term, immediate relief of heartburn. The varying salt formulations contribute to adverse effects, such as diarrhea or constipation.
- Chemotherapeutic agents directly activate the vomiting center (CTZ), and medications used for CINV include phenothiazines, 5-HT_3 receptor antagonists (for example, *ondansetron*), substance P/neurokinin-1 receptor antagonists (for example, *aprepitant*), corticosteroids, and second-generation antipsychotics.
- The muscarinic receptor antagonist *scopolamine* and H_1-receptor antagonists are useful in the management of general nausea and

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vomiting, as well as motion sickness.
- Antidiarrheal medications include agents that decrease motility, act as adsorbents, and modify fluid and electrolyte transport.
- Medications used in the treatment of constipation include various types of laxatives such as bulk laxatives, osmotic laxatives, and stimulant laxatives. Adverse effects, including the risk of cramping, of each formulation should be considered when selecting a medication.
- Irritable bowel syndrome (IBS) is a condition affected by diet and psychosocial modifications, and medications are chosen based on the predominant form of the syndrome (IBS-C, IBS-D, or mixed).
- Drugs used in the treatment of inflammatory bowel disease (IBD) include 5-aminosalicylates (5-ASAs), corticosteroids, immunomodulators, biologic agents, and JAK inhibitors.
- The 5-ASAs (*mesalamine*, *balsalazide*, and *olsalazine*) are similar in efficacy but differ in their release mechanisms and distribution within the GI tract.
- Corticosteroids, biologic agents, immunomodulators, and the JAK inhibitors can all increase the risk of infection due to immunosuppressant effects.

STUDY QUESTIONS

Choose the ONE best answer.

42.1A 68-year-old patient with cardiac failure is diagnosed with ovarian cancer. She begins using cisplatin but becomes nauseous and suffers from severe vomiting. Which of the following drugs would be most effective to counteract the emesis in this patient without exacerbating her cardiac problem?

A. Droperidol
B. Dolasetron
C. Prochlorperazine
D. Palonosetron

Correct answer = D. Palonosetron is a 5-HT_3 antagonist that is effective against drugs with high emetogenic activity, such as cisplatin. Although dolasetron is

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also in this category, its propensity to affect the heart makes it a poor choice for this patient. Droperidol has the potential to prolong the QTc interval and is only recommended for the treatment of postoperative nausea and vomiting. The antiemetic effect of prochlorperazine, a phenothiazine, is most beneficial against anticancer drugs with moderate to low emetogenic properties.

42.2 An elderly woman with a recent history of myocardial infarction is seeking a medication to help treat her occasional heartburn. She is currently taking several medications, including aspirin, clopidogrel, simvastatin, metoprolol, and lisinopril. Which of the following drugs should be avoided in this patient?

A. Calcium carbonate
B. Famotidine
C. Omeprazole
D. Nizatidine

Correct answer = C. Although all of the agents listed are appropriate for the treatment of heartburn, use of omeprazole should be avoided in this patient. Omeprazole may decrease the efficacy of clopidogrel because it inhibits the conversion of clopidogrel to its active form.

42.3 A 45-year-old woman complains of nightly severe persistent heartburn for the past 3 weeks and an unpleasant, acid-like taste in her mouth. The clinician suspects that she has gastroesophageal reflux disease. Which of the following drugs is most appropriate?

A. An antacid such as aluminum hydroxide
B. Dicyclomine
C. Granisetron
D. Omeprazole

Correct answer = D. Given the length of time and the severity of the heartburn, it is appropriate to treat this patient with a proton pump inhibitor (PPI) to reduce acid production and promote healing. An H_2 receptor antagonist might also be

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effective, but the PPIs are preferred. An antacid would decrease gastric acid, but its effects are short lived compared with those of the PPIs and H_2 receptor antagonists. Dicyclomine is an antimuscarinic drug that is mainly used as an antispasmodic for IBS. The 5-HT_3 receptor antagonist granisetron is an antiemetic and not appropriate for the treatment of GERD.

42.4 A couple celebrating their 30th wedding anniversary are given a trip to Peru to visit Machu Picchu. Because of past experiences while traveling, they ask their doctor to prescribe an agent in case they experience diarrhea. Which of the following drugs would be effective?

A. Omeprazole
B. Loperamide
C. Famotidine
D. Lubiprostone

Correct answer = B. Loperamide is the only drug that has antidiarrheal activity. Omeprazole is a proton pump inhibitor, famotidine antagonizes the H_2 receptor to reduce acid production, and lubiprostone is indicated for chronic constipation or IBS-C.

42.5 A 27-year-old woman who is 34 weeks' pregnant is on bed rest and is experiencing mild constipation. Which of the following drugs is most appropriate for her?

A. Castor oil
B. Docusate
C. Mineral oil
D. Loperamide

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Correct answer = B. Although its effects are not immediate, docusate may be used for mild constipation and is generally considered safe in pregnancy. Castor oil should not be used in pregnancy because of its ability to cause uterine contractions. Mineral oil should not be used in bedridden patients due to the possibility of aspiration. Loperamide is used for diarrhea, not constipation.

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42.6 A 25-year-old man with a past medical history of alcohol use disorder presents with IBS-D. He has tried various nonpharmacological approaches and continues to have bothersome cramping, especially during stressful situations. Which of the following may be considered as a treatment option for this patient?

A. Alosetron
B. Eluxadoline
C. Linaclotide
D. Dicyclomine

Correct answer = D. Dicyclomine is used in IBS-D and is particularly useful in decreasing GI spasms and motility. Alosetron is currently only approved for use in women. Eluxadoline should be excluded, given the history of alcohol use disorder. Linaclotide is used in IBS-C.

42.7 Extrapyramidal symptoms (EPS) have been associated with which of the following drugs?

A. Metoclopramide
B. Sucralfate
C. Aprepitant
D. Bisacodyl

Correct answer = A. Only metoclopramide has been associated with EPS. This is due to its ability to inhibit dopamine activity.

42.8 Which of the following agents for gastrointestinal problems is contraindicated in pregnancy?

A. Calcium carbonate
B. Famotidine
C. Lansoprazole
D. Misoprostol

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Correct answer = D. Misoprostol, a synthetic prostaglandin analog, is contraindicated in pregnancy because it may stimulate uterine contractions. The other medications may be used during pregnancy for the treatment of heartburn (common in pregnancy) or peptic ulcer disease.

42.9 A patient presents with a 2-month history of crampy right lower quadrant abdominal pain. Results of endoscopy are consistent with moderate Crohn disease involving the terminal ileum and proximal large intestine. Which of the following drugs is best to initiate in this patient at this time?

A. Extended-release budesonide
B. Delayed-release budesonide
C. Mesalamine enema
D. Ustekinumab

Correct answer = B. Delayed-release budesonide is indicated in Crohn disease because it releases in the terminal ileum and proximal large bowel and is effective in inducing remission. Extended-release budesonide, although effective at inducing remission, is only indicated in ulcerative colitis because it does not release in the small bowel and would not be expected to be effective in this patient's ileal disease. Mesalamine enema is only effective on the distal large intestine. Ustekinumab is only indicated in patients who are refractory or intolerant to TNF-α inhibitors.

42.10 A 63-year-old woman with Crohn disease has been started on infliximab with no response. She is deemed refractory, and other therapy is needed to induce remission. Which of the following options would be appropriate to initiate at this time?

A. Tofacitinib
B. Balsalazide
C. Methotrexate
D. Ustekinumab

Correct answer = D. Ustekinumab is the correct choice as it is recommended in patients refractory to TNF-α inhibitors such as infliximab. Tofacitinib is not

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indicated in Crohn disease. Balsalazide is a 5-ASA, which is generally ineffective and not recommended in Crohn disease. Methotrexate is not indicated for induction of remission since response would be delayed for months.

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43

Drugs for Urologic Disorders

Katherine Vogel Anderson, Kimberly Atkinson

I. OVERVIEW

Erectile dysfunction (ED), benign prostatic hyperplasia (BPH), and urinary incontinence are common urologic disorders. ED is the inability to maintain penile erection for the successful performance of sexual activity. ED may result from vascular disease, diabetes, medications, depression, or sequelae of prostatic surgery. It is estimated to affect more than 30 million men in the United States and 300 million worldwide. BPH is nonmalignant enlargement of the prostate, which occurs naturally as men age. As the prostate grows in size, lower urinary tract symptoms develop, which can significantly impact patient quality of life. A summary of drugs for the treatment of ED and BPH is provided in Figure 43.1. For information on drugs for the management of incontinence and overactive bladder, please refer to Chapter 5 (antimuscarinics) and Chapter 6 (β_3 agonists).

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Figure 43.1 Summary of drugs used for the treatment of urologic disorders.

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II. DRUGS USED TO TREAT ERECTILE DYSFUNCTION

Therapy for ED includes penile implants, intrapenile injections of *alprostadil*, intraurethral suppositories of *alprostadil*, and oral phosphodiesterase-5 (PDE-5) inhibitors. Because of the efficacy, ease of use, and safety of PDE-5 inhibitors, these drugs are first-line therapy for ED.

A. Phosphodiesterase-5 inhibitors

Several PDE-5 inhibitors, including *sildenafil* [sil-DEN-a-fil], *vardenafil* [var-DEN-na-fil], *tadalafil* [ta-DAL-a-fil], and *avanafil* [a-VAN-a-fil], are approved for the treatment of ED. [Note: *Sildenafil* and *tadalafil* are also indicated to treat pulmonary hypertension, although the dosage regimen differs for this indication.] All PDE-5 inhibitors are equally effective in treating ED, and the adverse effect profiles of the drugs are similar. However, these agents differ in the duration of action and the effects of food on drug absorption.

1. Mechanism of action: Sexual stimulation results in smooth muscle relaxation of the corpus cavernosum, increasing the inflow of blood (Figure 43.2). The mediator of this response is nitric oxide (NO). NO activates guanylyl cyclase, which forms cyclic guanosine monophosphate (cGMP) from guanosine triphosphate. cGMP produces smooth muscle relaxation through a reduction in the intracellular Ca^{2+} concentration. The duration of action of cyclic nucleotides (such as cGMP) is controlled by the action of phosphodiesterase (PDE). At least 11 isozymes of PDE have been characterized. *Sildenafil*, *vardenafil*, *tadalafil*, and *avanafil* inhibit PDE-5, the isozyme responsible for degradation of cGMP in the corpus cavernosum. Inhibition of PDE-5 prevents degradation of cGMP, thereby increasing blood flow into the corpus cavernosum with any given level of

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sexual stimulation. At recommended doses, PDE-5 inhibitors have no effect in the absence of sexual stimulation.

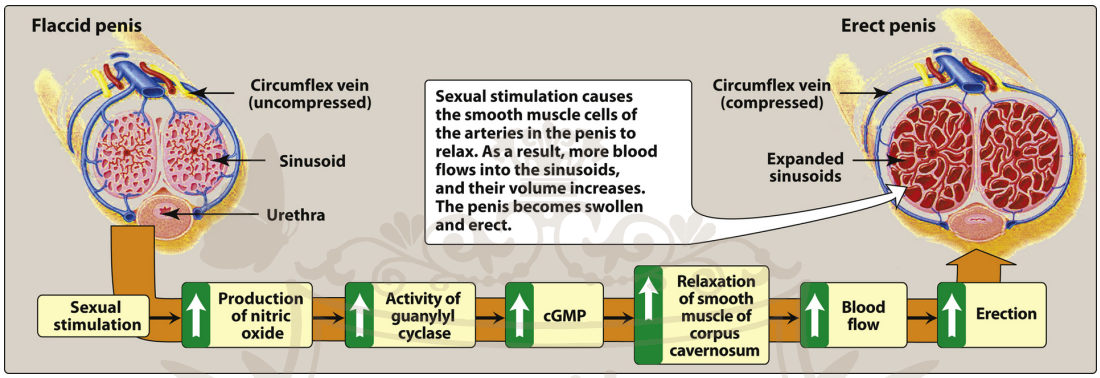

Figure 43.2 Mechanism of penile erection.cGMP = cyclic guanosine monophosphate.

2.Pharmacokinetics: *Sildenafil* and *vardenafil* have similar pharmacokinetic properties. Both drugs should be taken approximately 1 hour prior to anticipated sexual activity, with erectile enhancement observed for up to 4 hours after administration. Thus, administration of *sildenafil* and *vardenafil* must be timed appropriately with regard to anticipated sexual activity. The absorption of both drugs is delayed by the consumption of a high-fat meal. *Vardenafil* is also available in an orally disintegrating tablet (ODT) formulation, which is not affected by a high-fat meal. However, the bioavailability of the ODT formulation may be decreased by water, and therefore, the ODT should be placed under the tongue and not administered with liquids. The *vardenafil* ODT provides a higher systemic bioavailability than the *vardenafil* film-coated oral tablet, so the products are not interchangeable. *Tadalafil* has a slower onset of action (Figure 43.3) than *sildenafil* and *vardenafil*, but a significantly longer half-life of approximately 18 hours. As such, *tadalafil* is approved for once-daily dosing (in addition to as-needed dosing), and this results in enhanced

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erectile function for up to 36 hours. Furthermore, the absorption of *tadalafil* is not clinically influenced by food. The timing of sexual activity is less critical for *tadalafil* because of its prolonged duration of effect. Of all the PDE-5 inhibitors, *avanafil* has the quickest onset of action. It should be taken 30 minutes prior to sexual activity. All PDE-5 inhibitors are metabolized by the cytochrome P450 3A4 (CYP3A4) isoenzyme. Dosage adjustments for *sildenafil*, *tadalafil*, and *vardenafil* are recommended in patients with mild to moderate hepatic dysfunction. PDE-5 inhibitors should be avoided in patients with severe hepatic impairment. For patients with severe renal dysfunction, the dose of *sildenafil* and *tadalafil* should be reduced. *Avanafil* and daily-dose *tadalafil* are contraindicated in patients with severe renal dysfunction.

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A Time to peak concentration

Avanafil	30–45 min
Sildenafil	60 min
Vardenafil	60 min
Tadalafil	120 min

B Half-life

Avanafil	5 hr
Sildenafil	3–4 hr
Vardenafil	4–5 hr
Tadalafil	18 hr

C Food interaction*

Avanafil	No
Sildenafil	Yes
Vardenafil	Yes
Tadalafil	No

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Figure 43.3 Some properties of phosphodiesterase inhibitors.*Delay in time to reach peak drug concentration when taken with high-fat foods.

3.Adverse effects: The most frequent adverse effects of the PDE-5 inhibitors are headache, flushing, dyspepsia, and nasal congestion. These effects are generally mild, and men with ED rarely discontinue treatment because of side effects. Disturbances in color vision (loss of blue/green discrimination) may occur with PDE-5 inhibitors, likely due to the inhibition of PDE-6 (a PDE found in the retina that is important in color vision). *Tadalafil*, however, does not appear to disrupt PDE-6, and reports of changes in color vision have been rare with this medication. The incidence of these reactions appears to be dose-dependent. Sudden hearing loss has also been reported with the use of PDE-5 inhibitors, perhaps due to changes in sinus pressure because of vasodilation. *Tadalafil* has been associated with back pain and myalgias, likely because of inhibition of PDE-11, an enzyme found in skeletal muscle. There is an inherent cardiac risk associated with sexual activity. Therefore, PDE-5 inhibitors should be used with caution in patients with a history of cardiovascular disease or those with strong risk factors for cardiovascular disease. PDE-5 inhibitors should not be used more than once per day for the treatment of ED. All of the PDE-5 inhibitors have the potential to cause priapism, a painful, prolonged erection. Although this is a rare side effect, it is a medical emergency.

Clinical Application 43.1: Treatment of Ischemic Priapism

Priapism is defined by the American Urological Association (AUA) as a persistent penile erection that continues hours beyond, or is unrelated to, sexual stimulation. Priapism is considered a medical emergency and requires prompt evaluation. There are three types of priapism: ischemic, nonischemic, and stuttering (intermittent). Ischemic priapism is typically caused by ED medications and presents as a corpus cavernosum that is fully rigid, penile pain,

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and abnormal cavernous blood gases. Ischemic priapism is first treated with therapeutic aspiration, with or without irrigation. If ischemic priapism persists, intracavernous injection of sympathomimetic drugs is indicated. The AUA recommends *phenylephrine* as a first-line treatment, as it has a lower incidence of cardiovascular adverse effects compared to other sympathomimetic medications such as *epinephrine*, *norepinephrine*, and *ephedrine.* One milliliter of *phenylephrine* (diluted to a concentration of 100-500 µg/mL) should be administered every 3 to 5 minutes for up to 1 hour. If treatment with *phenylephrine* is unsuccessful, surgical shunts may be considered for the management of ischemic priapism.

4.Drug interactions: Because of the ability of PDE-5 inhibitors to potentiate the hypotensive activity of NO, administration of these medications in combination with organic nitrates (for example, *nitroglycerin* products, *isosorbide dinitrate*, or *isosorbide mononitrate*) is contraindicated. PDE-5 inhibitors may produce additive blood pressure–lowering effects in patients taking α-adrenergic antagonists for treatment of hypertension and/or alleviation of symptoms associated with BPH. The combination of PDE-5 inhibitors and α-adrenergic antagonists should be used with caution. Patients should be on a stable dose of the α-adrenergic antagonist prior to initiation of the PDE-5 inhibitor, and the PDE-5 inhibitor should be started at the lowest dose if this combination is used. Doses of PDE-5 inhibitors may need to be reduced in the presence of potent inhibitors of CYP3A4, such as *clarithromycin* and *ritonavir* or other protease inhibitors. Because of the risk for QT prolongation, use of *vardenafil* is contraindicated with *dronedarone* and *fluconazole.* Caution should be used when prescribing *vardenafil* with other agents associated with QT prolongation.

B. Alprostadil

Alprostadil [al-PRAHST-uh-dill] is a synthetic prostaglandin E1 (PGE1). In the penile tissue, PGE1 allows for relaxation of the smooth muscle in the corpus cavernosum. *Alprostadil* is available

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as an intraurethral suppository and an injectable formulation. Since PDE-5 inhibitors are considered first-line therapy for the treatment of ED, *alprostadil* may be used for patients who are not candidates for oral therapies. In contrast to oral agents, *alprostadil* acts locally, which may reduce the occurrence of adverse effects.

1. **Mechanism of action:** *Alprostadil* causes smooth muscle relaxation by an unknown mechanism. It is believed that *alprostadil* increases concentrations of cyclic adenosine monophosphate (cAMP) within cavernosal tissue. As a result, protein kinase is activated, allowing trabecular smooth muscle relaxation and dilation of cavernosal arteries. Increased blood flow to the erection chamber compresses venous outflow, so that blood is entrapped and erection may occur.

2. **Pharmacokinetics:** Systemic absorption of *alprostadil* is minimal. If any *alprostadil* is systemically absorbed, it is quickly metabolized. The onset of action of *alprostadil* is 5 to 10 minutes when given as a urethral suppository and 2 to 25 minutes when administered by injection. The resulting erection may last for 30 to 60 minutes, or longer, depending upon the particular patient.

3. **Adverse effects:** Since *alprostadil* is not systemically absorbed, adverse systemic effects are rare. However, hypotension or headache is a possibility due to PGE1-induced vasodilation. Locally, adverse effects of *alprostadil* include penile pain, urethral pain, and testicular pain. Bleeding from the insertion or injection of *alprostadil* is rare. Hematoma, ecchymosis, and rash are possible from *alprostadil* injection, although these adverse effects are also rare. *Alprostadil* administration may lead to priapism.

III. BENIGN PROSTATIC HYPERPLASIA

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Three classes of medications are used to treat BPH: α_1-adrenergic antagonists, 5α-reductase inhibitors, and PDE-5 inhibitors.

A. α_1-adrenergic antagonists

Terazosin [ter-AY-zoe-sin], *doxazosin* [dox-AY-zoe-sin], *tamsulosin* [tam-SUE-loh-sin], *alfuzosin* [al-FUE-zoe-sin], and *silodosin* [sil-oh-DOE-sin] are selective competitive blockers of the α_1 receptor. All five agents are indicated for the treatment of BPH (Figure 43.1). *Prazosin* is an α-blocker that is used off-label in the treatment of BPH. However, current guidelines do not endorse the use of *prazosin* for BPH. Please refer to Chapter 7 for a discussion of α-blockers in the setting of hypertension.

1. Mechanism of action: α_{1A} receptors are found in the prostate, α_{1B} receptors are found in the prostate and vasculature, and α_{1D} receptors are found in the vasculature. By blocking the α_{1A} and α_{1B} receptors in the prostate, the α-blockers cause prostatic smooth muscle relaxation, which leads to improved urine flow. *Doxazosin*, *terazosin*, and *alfuzosin* block α_{1A} and α_{1B} receptors, whereas *tamsulosin* and *silodosin* are more selective for the α_{1A} receptor. Because *doxazosin*, *terazosin*, and *alfuzosin* block α_{1B} receptors, these agents decrease peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial and venous smooth muscle. By contrast, *tamsulosin* and *silodosin* have less effect on blood pressure because they are more selective for the prostate-specific α_{1A} receptor.

2. Pharmacokinetics: The α-blockers are well absorbed following oral administration. For best efficacy, *tamsulosin, alfuzosin*, and *silodosin* should be administered with food. *Doxazosin* and *terazosin* may be taken without regard to food. *Doxazosin*, *alfuzosin*, *tamsulosin*, and *silodosin* are metabolized through the cytochrome P450 system. *Silodosin* is also a substrate for P-glycoprotein (P-gp). *Terazosin* is

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metabolized in the liver, but not through the CYP system. In general, the α-blockers have a half-life of 8 to 22 hours, with peak effects 1 to 4 hours after administration. *Silodosin* requires dosage adjustment in renal impairment and is contraindicated in patients with severe renal dysfunction.

3.Adverse effects: α-Blockers may cause dizziness, a lack of energy, nasal congestion, headache, drowsiness, and orthostatic hypotension (Figure 43.4). Because *tamsulosin* and *silodosin* are more selective for the α_{1A} receptors found on the smooth muscle of the prostate, they have relatively minimal effects on blood pressure, although dizziness and orthostasis may occur. While they have fewer systemic side effects, the agents with more prostate selectivity are associated with an increased incidence of retrograde ejaculation or the inability to ejaculate. Several of these agents have a caution about intraoperative “floppy iris syndrome,” a condition in which the iris billows in response to cataract eye surgery.

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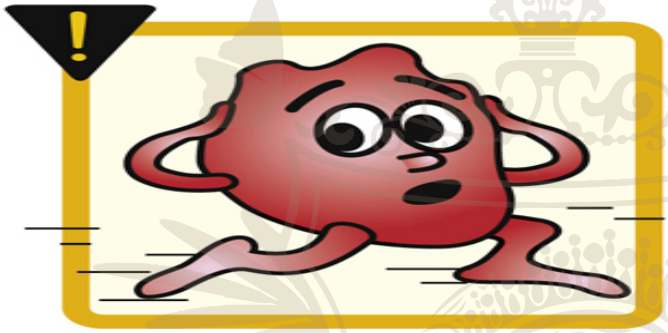
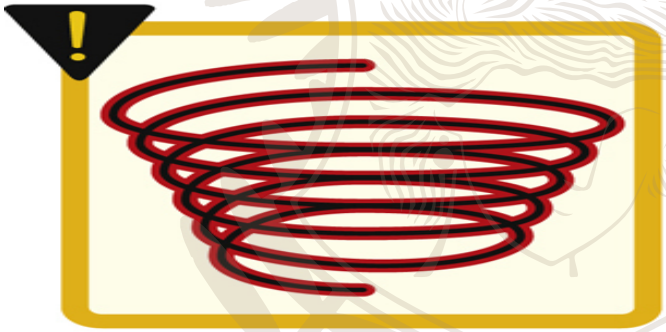
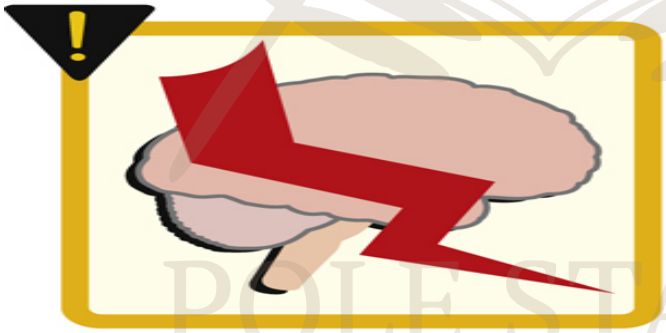
Orthostatic hypotension



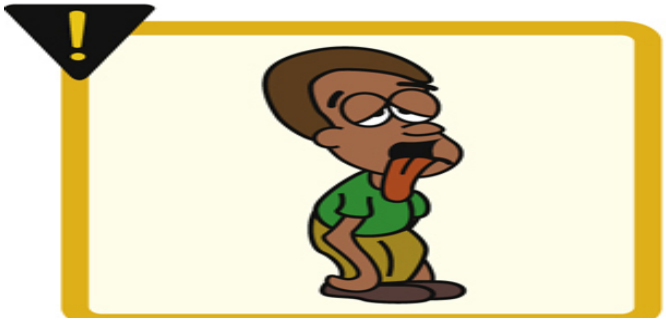
Tachycardia



Vertigo



Headache



Fatigue

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Figure 43.4 Some adverse effects commonly observed with nonselective α-blockers.

4. Drug interactions: Drugs that inhibit CYP3A4 and CYP2D6 (for example, *verapamil*, *diltiazem*) may increase the plasma concentrations of *doxazosin*, *alfuzosin*, *tamsulosin*, and *silodosin*, whereas drugs that induce the CYP450 system (for example, *carbamazepine*, *phenytoin*, and *St. John's wort*) may decrease plasma concentrations. *Alfuzosin* may prolong the QT interval, so it should be used with caution with other drugs that cause QT prolongation (for example, class III antiarrhythmics). Because *silodosin* is a substrate for P-gp, drugs that inhibit P-gp, such as *cyclosporine*, may increase *silodosin* concentrations.

B. 5α-reductase inhibitors

Finasteride [fin-AS-ter-ide] and *dutasteride* [doo-TAS-ter-ride] inhibit 5α-reductase. Compared to the α-blockers, which provide patients with relief from BPH symptoms within 7 to 10 days, these agents generally take 6 to 12 months to relieve symptoms.

1. Mechanism of action: Both *finasteride* and *dutasteride* inhibit the enzyme 5α-reductase, which is responsible for converting *testosterone* to the more active *dihydrotestosterone* (DHT). DHT is an androgen that stimulates prostate growth. By reducing DHT, the prostate shrinks and urine flow improves. Compared with *finasteride*, *dutasteride* is more potent and causes a greater decrease in DHT. In order for the 5α-reductase inhibitors to be effective, the prostate must be enlarged. Since it takes several months for 5α-reductase inhibitors to reduce the prostate size, it is appropriate to use these agents in combination with an α-blocker to provide relief of symptoms. *Dutasteride* and *tamsulosin* are available as a combination product for this indication. Figures 43.5 and 43.6

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summarize important differences between these two classes of agents. [Note: *Finasteride* and *dutasteride* are also used for alopecia, since a reduction in scalp and serum DHT prevents hair loss.]

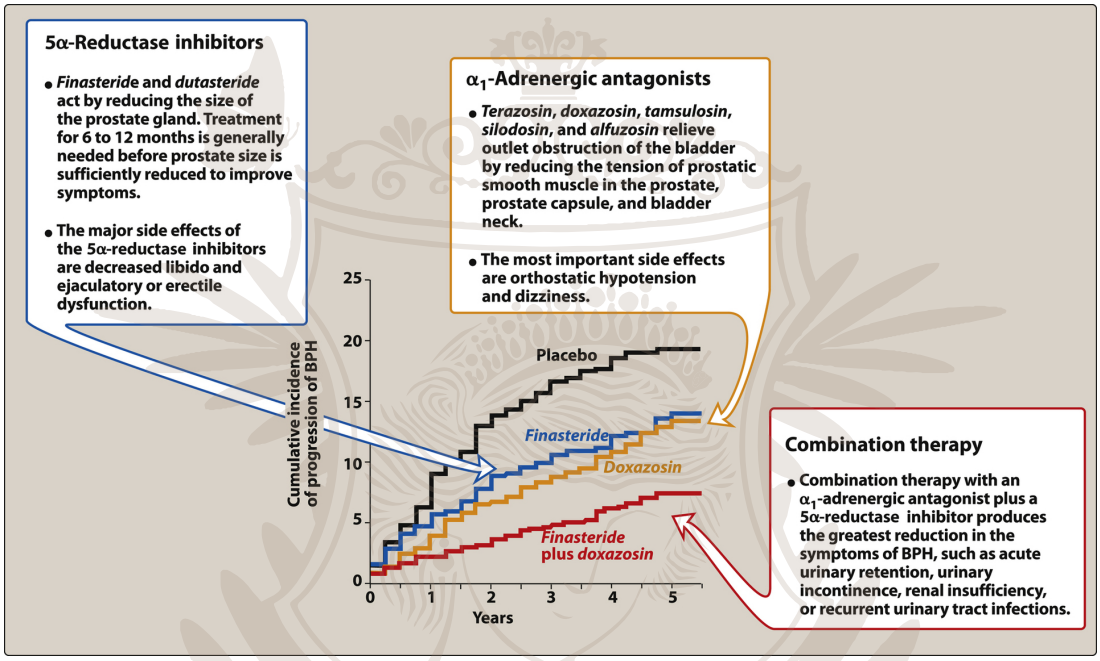

Figure 43.5 Therapy for benign prostatic hyperplasia (BPH).

	α_1-ADRENERGIC ANTAGONISTS	5 α-REDUCTASE INHIBITORS
Decrease in prostate size	No	Yes
Peak onset	2–4 weeks	6–12 months
Decrease in PSA	No	Yes
Sexual dysfunction	+	++
Hypotensive effects	++	–
Commonly used drugs	*Tamsulosin* and *alfuzosin*	*Finasteride* and *dutasteride*

Figure 43.6 Comparisons of treatment for benign prostatic hyperplasia.PSA = prostate-specific antigen.

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2.Pharmacokinetics: Food does not affect the absorption of *finasteride* or *dutasteride.* Both agents are highly protein bound and metabolized by the CYP450 system. The mean plasma elimination half-life of *finasteride* is 6 to 16 hours, while the terminal elimination half-life of *dutasteride* is 5 weeks once steady-state concentrations are achieved (which is typically after 6 months of therapy).

3.Adverse effects: The 5α-reductase inhibitors cause sexual side effects, such as decreased ejaculate, decreased libido, ED, gynecomastia, and oligospermia. *Finasteride* and *dutasteride* are teratogenic. Women who are pregnant or of childbearing age should not handle or ingest either agent, as this may lead to serious birth defects involving the genitalia in a male fetus. Although both agents are metabolized by the CYP450 system, drug interactions are rare. It is not ideal to use a 5α-reductase inhibitor with *testosterone*, since both *finasteride* and *dutasteride* inhibit the conversion of *testosterone* to its active form, DHT.

C. Phosphodiesterase-5 inhibitor

Tadalafil is the only PDE-5 inhibitor approved for the treatment of BPH. PDE-5 is present in the prostate and bladder. As such, inhibition of PDE-5 by *tadalafil* allows for vasodilation and relaxation of the smooth muscle of the prostate and bladder, which thereby improves symptoms of BPH.

Chapter Summary

- PDE-5 inhibitors (*avanafil*, *sildenafil*, *tadalafil*, *and vardenafil*) are first-line agents for the treatment of ED. In the setting of sexual stimulation, PDE-5 inhibitors allow increased blood flow into the corpus cavernosum by inhibiting PDE-5 and thereby increasing cGMP.
- PDE-5 inhibitors potentiate the hypotensive activity of nitric oxide. Therefore, co-administration of PDE-5 inhibitors with nitrates is contraindicated because of the potential to cause life-threatening hypotension.

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- *Alprostadil*, a synthetic prostaglandin, is a second-line treatment of ED and is administered as a suppository or an injection. *Alprostadil* increases cAMP within cavernosal tissue, causing smooth muscle relaxation and dilation of cavernosal arteries.
- All of the drugs used to treat ED can cause priapism. Although rare, priapism is a medical emergency which warrants immediate attention.
- The α_1-adrenergic antagonists (*alfuzosin*, *doxazosin*, *silodosin*, *tamsulosin*, *terazosin*) are used to treat symptoms of BPH. By blocking α receptors in the prostate, α_1-adrenergic antagonists allow smooth muscle relaxation and improved urine flow.
- *Alfuzosin*, *doxazosin*, and *terazosin* block α_{1A} and α_{1B} receptors (nonselective), while *tamsulosin* and *silodosin* block α_{1A} receptors (selective for the prostate). Selective α-blockers have a lower incidence of systemic side effects, such as orthostatic hypotension, dizziness, and headache, but have an increased incidence of retrograde or anejaculation.
- The 5α-reductase inhibitors *finasteride* and *dutasteride* inhibit the conversion of testosterone to DHT, which, in turn, decreases prostate growth. 5α-Reductase inhibitors are only effective if the prostate is enlarged and may take 6 to 12 months to show efficacy. *Finasteride* and *dutasteride* are teratogenic; both are contraindicated in pregnancy, and women of childbearing age should not handle either medication.
- It is appropriate to treat BPH with a combination of an α-blocker and a 5α-reductase inhibitor for patients who have BPH symptoms and a significantly enlarged prostate.

STUDY QUESTIONS

Choose the ONE best answer.

43.1A 68-year-old man presents to his physician with complaints of inability to maintain an erection during sexual intercourse. He is diagnosed with erectile dysfunction and started on a PDE-5 inhibitor. What is its mechanism of action in the treatment of ED?

A. Cause an erection in the absence of sexual stimulation
B. Block the degradation of cGMP in the corpus cavernosum

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C. Decrease blood flow into the corpus cavernosum
D. Antagonize the effects of nitric oxide

Correct answer = B. PDE-5 inhibition blocks the degradation of cGMP. Without sexual stimulation, PDE-5 inhibitors will not cause an erection. Because PDE-5 inhibitors enhance vasodilation, blood flow is increased into the corpus cavernosum. PDE-5 inhibitors enhance the effect of nitric oxide by preventing the breakdown of cGMP.

43.2 A patient who is taking a PDE-5 inhibitor for ED is diagnosed with angina. Which of the following antianginal medications would be of particular concern in this patient?

A. Metoprolol
B. Diltiazem
C. Amlodipine
D. Nitroglycerin

Correct answer = D. Nitrates such as nitroglycerin can cause life-threatening hypotension when taken with PDE-5 inhibitors. While metoprolol, diltiazem, and amlodipine may all lower blood pressure, the interaction with PDE-5 inhibitors is not relevant.

43.3 Which of the following statements most accurately describes alprostadil in the treatment of ED?

A. Used as an alternative for patients who are not candidates for oral therapies for ED
B. Has a higher rate of systemic side effects compared to PDE-5 inhibitors
C. Does not cause priapism
D. Should be taken with food to increase absorption

Correct answer = A. Alprostadil, available as an intraurethral suppository or an injection, acts locally. This makes it ideal for patients who cannot take oral medications. Because alprostadil is locally administered, systemic absorption is minimal, which leads to a lower rate of systemic side effects when compared to

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PDE-5 inhibitors. However, alprostadil may still cause priapism. Because alprostadil acts locally, it does not need to be taken with regard to food.

43.4 Which of the following enzymes or receptors does tamsulosin block to aid in the treatment of benign prostatic hyperplasia?

A. 5α-Reductase
B. α_{1A} receptor
C. PDE-5
D. α_{1B} receptor

Correct answer = B. Tamsulosin blocks α_{1A} receptors. Tamsulosin does not affect 5α-reductase, α_{1B} receptors, or PDE-5.

43.5 A patient is worried about starting a new medication to treat his BPH because he is very sensitive to side effects of medications. Which of the following α_1-adrenergic antagonists could be recommended because of a lower incidence of systemic side effects?

A. Doxazosin
B. Alfuzosin
C. Silodosin
D. Terazosin

Correct answer = C. Doxazosin, terazosin, and alfuzosin block α_{1A} and α_{1B} receptors, whereas silodosin is more selective for the α_{1A} receptor. Blocking the α_{1B} receptor decreases peripheral vascular resistance and lowers arterial blood pressure. By doing this, α_{1B}-blockers may cause dizziness, a lack of energy, and orthostatic hypotension. Silodosin is more selective for the α_{1A} receptors found on the smooth muscle of the prostate, thus having minimal effects on blood pressure compared to the less selective agents.

43.6 A 74-year-old patient presents to his PCP to discuss treatment for ED. His current medications include furosemide,

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isosorbide dinitrate, lisinopril, metformin, and metoprolol succinate. Which of the following would be the safest option to treat ED?

A. Tadalafil
B. Alprostadil
C. Sildenafil
D. Vardenafil

Correct answer = B. Because of the ability of PDE-5 inhibitors to potentiate the hypotensive activity of nitric oxide, administration of a PDE-5 inhibitor in combination with isosorbide dinitrate is contraindicated. Alprostadil is synthetic PGE1 which is not systemically absorbed and adverse systemic effects are rare. Therefore, the safest option to use for this patient is alprostadil.

43.7A patient with BPH has been taking finasteride for 6 weeks. He reports no improvement in symptoms of urinary frequency, hesitancy, and urgency. On physical examination, it is determined that his prostate is significantly enlarged. Which of the following is the best recommendation for this patient?

A. Start tamsulosin and continue finasteride.
B. Stop finasteride and start doxazosin.
C. Switch from finasteride to dutasteride.
D. Add dutasteride in addition to finasteride.

Correct answer = A. It can take several months for finasteride to reduce prostate size and reduce symptoms of BPH. As such, it is appropriate to use an α-blocker in combination with finasteride to provide relief of symptoms. Because the patient's prostate is enlarged, he should continue therapy with finasteride. There is no reason to switch from finasteride to dutasteride since both are equally effective. Similarly, it would be inappropriate for this patient to take two 5α-reductase inhibitors since both have the same mechanism of action.

43.8A 70-year-old man with BPH and an enlarged prostate continues to have urinary symptoms after an adequate trial of

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tamsulosin. He is diagnosed with ED. Which medication can be used to treat both BPH and ED in this patient?

A. Avanafil
B. Sildenafil
C. Tadalafil
D. Vardenafil

Correct answer = C. Tadalafil is the only PDE-5 inhibitor approved for the treatment of ED and BPH.

43.9 A patient who is currently being treated for ED with tadalafil tells the physician that the medication takes too long to work. As such, he would like an alternative that has a faster onset of action. Which of the following PDE-5 inhibitors would be the most appropriate alternative for this patient?

A. Sildenafil
B. Finasteride
C. Avanafil
D. Vardenafil

Correct answer = C. Sildenafil and vardenafil should be taken approximately 1 hour prior to anticipated sexual activity, thus administration must be timed appropriately with regard to sexual activity. Finasteride is not used for ED. Avanafil has the quickest onset of action and should be taken 30 minutes prior to sexual activity.

43.10 Which of the following is the CORRECT mechanism of action of finasteride?

A. Converts dihydrotestosterone to testosterone
B. Inhibits 5α-reductase
C. Inhibits α receptors in the prostate
D. Blocks PDE-5

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Correct answer = B. 5α-Reductase is the enzyme that converts testosterone to DHT. Therefore, blocking 5α-reductase reduces the conversion of testosterone to DHT. Finasteride has no effect on α receptors or PDE-5.

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44

Drugs for Anemia

Jamie K. Alan

I. OVERVIEW

Anemia is defined as a below-normal plasma hemoglobin concentration resulting from a decreased number of circulating red blood cells or an abnormally low total hemoglobin content per unit of blood volume. General signs and symptoms of anemia include fatigue, palpitations, shortness of breath, pallor, dizziness, and insomnia. Anemia can be caused by acute or chronic blood loss, bone marrow abnormalities, hemolysis, infections, drugs, malignancy, endocrine deficiencies, renal failure, and a number of other disease states. A large number of drugs cause toxic effects on blood cells, hemoglobin production, or erythropoietic organs, which, in turn, may cause anemia. Nutritional anemias are caused by dietary deficiencies of substances such as iron, *folic acid*, and vitamin B_{12} (*cyanocobalamin*) that are necessary for normal erythropoiesis. Individuals with a genetic predisposition to anemia, such as sickle cell disease, can benefit from pharmacologic treatment with actions beyond nutritional supplementation, such as *hydroxyurea* or new biologic agents such as *crizanlizumab.* Anemia can be temporarily corrected by transfusion of whole blood or packed red blood cells. A summary of agents used for the treatment of anemias is provided in Figure 44.1.

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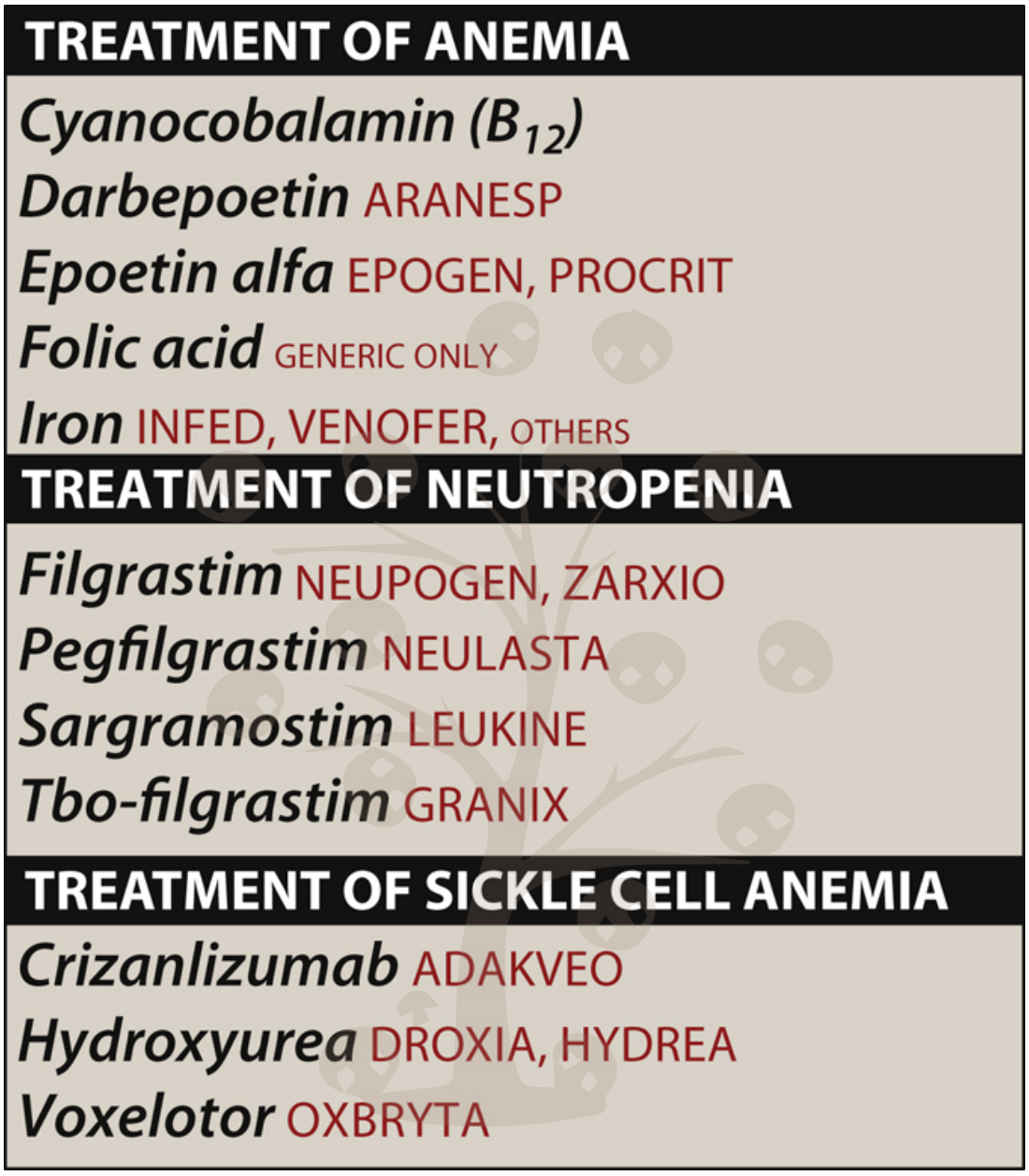

Figure 44.1 Summary of drugs for the treatment of anemia.

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II. AGENTS USED TO TREAT ANEMIAS

A. Iron

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Iron is stored in the intestinal mucosal cells, liver, spleen, and bone marrow as ferritin (an iron–protein complex) and delivered to the marrow for hemoglobin production by transferrin, a transport protein. Iron deficiency, the most common nutritional deficiency, results from a negative iron balance due to depletion of iron stores and/or inadequate intake, such as acute or chronic blood loss, menstruation, pregnancy, or periods of accelerated growth in children. In addition to general signs and symptoms of anemia, iron deficiency anemia may cause pica (hunger for ice, dirt, paper, etc.), koilonychias (upward curvature of the fingernails and toenails), and soreness and cracking at the corners of the mouth.

Clinical Application 44.1 Initial Evaluation of Iron Deficiency Anemia

It is fairly common for premenopausal women to present with iron deficiency anemia. Menstruation can be a benign physiologic reason behind this anemia. Iron deficiency anemia can also be caused by other reasons including dietary deficiencies or overt blood loss. Men and postmenopausal women without a history of overt bleeding who present with iron deficiency anemia should receive an endoscopy and a colonoscopy. In these populations, there is an increased chance of malignancy or other gastrointestinal (GI) pathologies.

1.Mechanism of action: Supplementation with elemental iron corrects the iron deficiency. The CDC recommends 60 to 120 mg/day of oral elemental iron administered in divided doses two to three times daily to treat patients with iron deficiency anemia. In pregnant women, 30 mg/day of iron may be given to meet increased nutritional needs, even in patients with a normal hemoglobin and hematocrit. While these doses are currently recommended, newer studies have shown that higher doses of iron (60-120 mg/day) may not be any more effective than lower dosages (40-80 mg/day). In fact, some studies suggest that higher dosages of iron can paradoxically decrease iron absorption. Furthermore, lower dosages of oral iron are less likely to produce bothersome side effects,

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resulting in better adherence to treatment. Every-other-day iron dosing is also emerging as a viable treatment option for iron deficiency anemia. This type of dosing has been shown to be equivalent to once-daily dosing and also results in fewer observed side effects.

2.Pharmacokinetics: Iron is absorbed after oral administration. Acidic conditions in the stomach keep iron in the reduced ferrous form, which is the more soluble form. Iron is then absorbed in the duodenum. [Note: The amount absorbed depends on the current body stores of iron. If iron stores are adequate, less iron is absorbed. If stores are low, more iron is absorbed.] The relative percentage of iron absorbed decreases with increasing doses. Oral preparations include *ferrous sulfate*, *ferrous fumarate*, *ferrous gluconate*, *polysaccharide–iron complex*, and *carbonyl iron* formulations. The percentage of elemental iron varies in each oral iron preparation (Figure 44.2). Parenteral formulations of iron, such as *iron dextran*, *sodium ferric gluconate*, *ferumoxytol*, *ferric carboxymaltose*, and *iron sucrose*, are also available. While parenteral administration treats iron deficiency rapidly, oral administration may take several weeks to correct the iron deficiency.

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IRON FORMULATION	BRAND NAME(S)	ELEMENTAL IRON (%)	NOTES
Ferrous gluconate	Fergon, Ferro-Tab	12	• Less elemental iron, but similar tolerability to *ferrous sulfate*
Ferric ammonium citrate	Iron citrate	18	• Less bioavailable than ferrous salts • Must be reduced to ferrous form in the intestine
Ferrous sulfate	Fer-in-Sol, Feratab	20	• Most common oral iron supplement • Low cost with good effectiveness and tolerability
Ferrous sulfate, anhydrous	Slow-Fe	30	• Extended-release formulation of *ferrous sulfate* (once-daily dosing) • Higher cost than *ferrous sulfate*
Ferrous fumarate	Ferretts, Ferrimin, Hemocyte	33	• Similar effectiveness and tolerability to *ferrous sulfate* • Almost no taste compared to other iron salts
Carbonyl iron	Icar, Feosol	100	• Microparticles of purified iron • Dissolves in the stomach to form HCl salt to be absorbed • Less toxic than iron salts due to slower absorption rate (continued iron release for 1 to 2 days)
Polysaccharide-iron complex	Bifera, NovaFerrum, Nu-Iron 150	100	• Tasteless and odorless • Once-daily elemental iron dose similar to twice-daily *ferrous sulfate*

Figure 44.2 Characteristics of various iron formulations.

3.Adverse effects: GI disturbances caused by local irritation (abdominal pain, constipation, nausea, diarrhea) and dark stools are the most common adverse effects of oral iron supplements. Parenteral iron formulations may be used in patients who cannot tolerate or inadequately absorb oral iron, as well as those receiving *erythropoietin* with hemodialysis or chemotherapy. Rare but potentially fatal hypersensitivity and anaphylactoid reactions can occur in patients receiving parenteral iron (mainly *iron dextran* formulations). A test dose should be administered prior to administering a full dose of *iron dextran.* In addition, intravenous iron should be used cautiously in the presence of active infections. [Note: Iron is essential for bacterial growth.]

Clinical Application 44.2: When to Use Parenteral Iron

While *iron dextran* does have a risk of significant adverse reactions, newer parenteral iron formulations (such as *sodium ferric gluconate*, *ferumoxytol*, *ferric carboxymaltose*, and *iron sucrose*) are much safer in this regard. A test dose of any parenteral iron formulation should be given to the patient before

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administration of a full dose. This test dose can be given over 5 to 30 min, and the patient should be observed for any side effects such as an allergic anaphylactic reaction. Administration of IV iron is more efficient at replenishing iron stores and replaces iron stores more quickly compared to oral iron. Parenteral iron therapy should be considered in patients who poorly tolerate oral iron, in patients who have malabsorption disease, end-stage renal disease (ESRD), or in patients with ongoing blood loss that cannot be managed with oral iron supplementation.

B. Folic acid (folate)

The primary use of *folic acid* is in treating deficiency states that arise from inadequate levels of the vitamin. Folate deficiency may be caused by (1) increased demand (for example, pregnancy and lactation), (2) poor absorption caused by pathology of the small intestine, (3) alcoholism, or (4) treatment with drugs that are dihydrofolate reductase inhibitors (for example, *methotrexate* and *trimethoprim*), drugs that directly inhibit DNA synthesis (for example, *azathioprine* and *zidovudine*), or drugs that reduce folate absorption (for example, *phenytoin* and *phenobarbital*). A primary result of *folic acid* deficiency is megaloblastic anemia (large-sized red blood cells, characterized by an increase in mean corpuscular volume [MCV]), which is caused by diminished synthesis of purines and pyrimidines. This leads to an inability of erythropoietic tissue to make DNA and, thereby, proliferate (Figure 44.3). [Note: To avoid neurologic complications of vitamin B_{12} deficiency, it is important to evaluate the basis of the megaloblastic anemia prior to instituting empiric therapy. Both vitamin B_{12} and folate deficiency can cause similar symptoms.]

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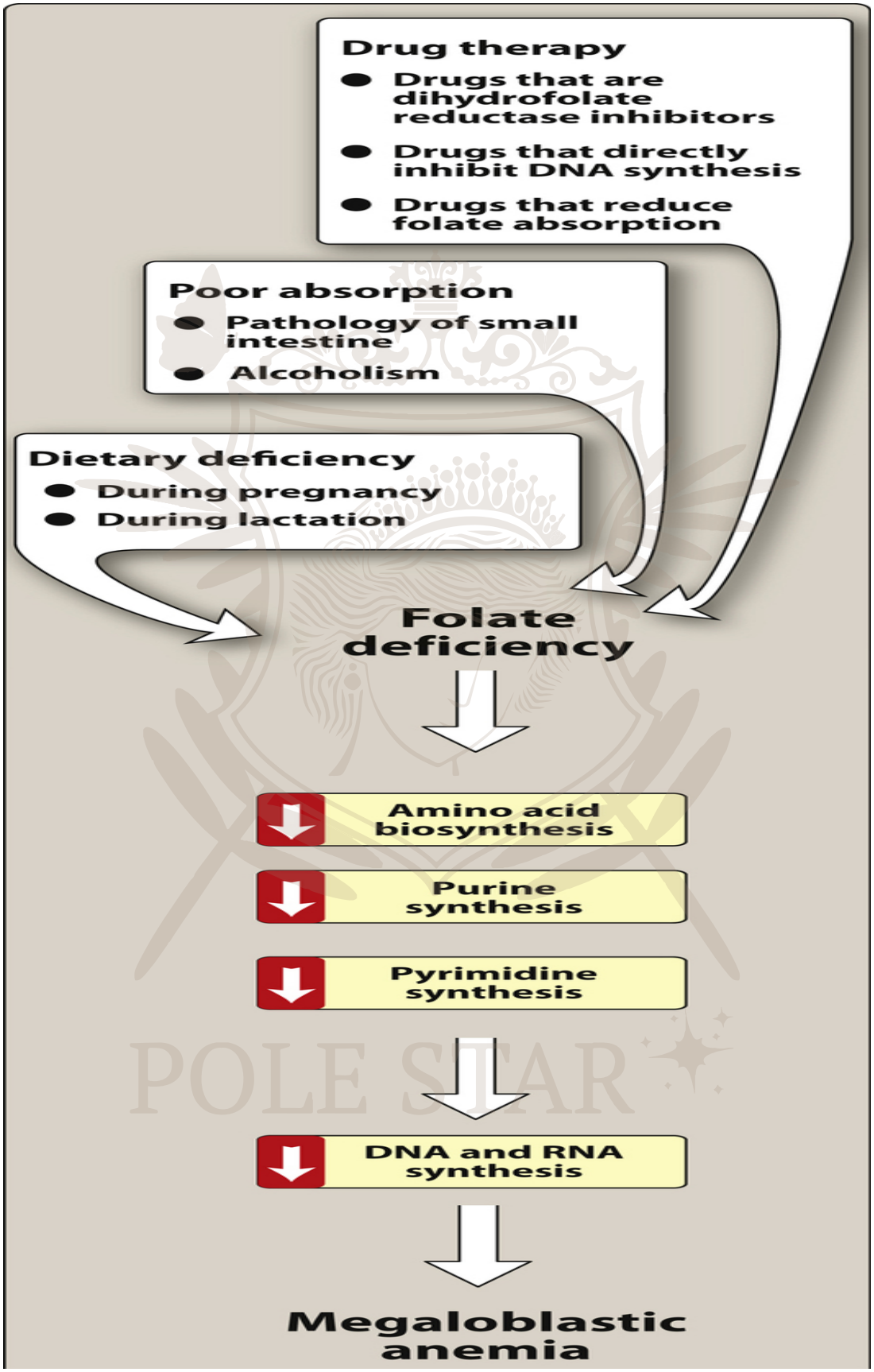

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Figure 44.3 Causes and consequences of *folic acid* depletion.

Folic acid is rapidly absorbed in the jejunum unless abnormal pathology is present. Oral *folic acid* administration is nontoxic and at high doses, excess vitamin is excreted in the urine. Rare hypersensitivity reactions to parenteral injections have been reported.

C. Cyanocobalamin and hydroxocobalamin (vitamin B_{12})

Deficiencies of vitamin B_{12} can result from either low dietary levels or, more commonly, poor absorption of the vitamin due to the failure of gastric parietal cells to produce intrinsic factor (as in pernicious anemia) or a loss of activity of the receptor needed for intestinal uptake of the vitamin. Nonspecific malabsorption syndromes or gastric resection can also cause vitamin B_{12} deficiency. In addition to general signs and symptoms of anemia, vitamin B_{12} deficiency anemia may cause tingling (pins and needles) in the hands and feet, difficulty walking, dementia, and, in extreme cases, hallucinations, paranoia, or schizophrenia. [Note: *Folic acid* administration alone reverses the hematologic abnormality and, thus, masks the vitamin B_{12} deficiency, which can then proceed to severe neurologic dysfunction and disease. The cause of megaloblastic anemia needs to be determined in order to be specific in terms of treatment. Therefore, empiric treatment of megaloblastic anemia should not be instituted with *folic acid* alone but, rather, with a combination of *folic acid* and *vitamin* B_{12} unless confirmatory tests are run.]

Vitamin B_{12} may be administered orally (for dietary deficiencies), sublingually, intramuscularly, or subcutaneously (for pernicious anemia). Intramuscular *hydroxocobalamin* [hye-drox-oh-koe-BAL-a-min] is preferred since it has a rapid response, is highly protein bound, and maintains longer plasma levels. In patients with malabsorption, such as in bariatric surgery (surgical treatment for

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obesity), vitamin B_{12} supplementation as *cyanocobalamin* [sye-an-oh-koe-BAL-a-min] is required as daily sublingual doses or monthly via parenteral administration. This vitamin is nontoxic even in large doses. In pernicious anemia, therapy must be continued for life.

Clinical Application 44.3 Evaluation of Megaloblastic Anemia

Megaloblastic anemia is a form of anemia characterized by abnormally large blood cells (above the upper limit for normal MCV). The most common cause for this type of anemia is a deficiency in either folate or vitamin B_{12}. Among other reasons, these deficiencies can be caused by an increased demand (pregnancy), drug therapy (for example, *methotrexate*), and dietary deficiencies. Vitamin B_{12} deficiency can also be caused by a lack of intrinsic factor, which is a co-factor for vitamin B_{12} absorption. If megaloblastic anemia is suspected, patients should be empirically treated with both folate and vitamin B_{12}. If folate is given alone, it may reverse the hematologic abnormalities; however, the subsequent vitamin B_{12} deficiency could go on to cause neurologic complications. Therefore, targeted treatment for megaloblastic anemia should only be given once a full workup of the patient is complete. To distinguish between a vitamin B_{12} and a folate deficiency, serum vitamin B_{12} and serum folate levels can be ordered. If the results from these tests are borderline, intermediates in vitamin B_{12} and folate metabolism (methylmalonic acid [MMA] and homocysteine) can be measured. If MMA and homocysteine are normal, there is no deficiency in either vitamin B_{12} or folate. If MMA and homocysteine are high, there is likely a B_{12} deficiency, but a folate deficiency cannot be ruled out. If MMA is normal but homocysteine is high, there is no deficiency in vitamin B_{12}, but a folate deficiency is likely. A patient with pernicious anemia would likely have a low serum vitamin B_{12} level and high MMA and homocysteine levels.

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D. Erythropoietin and darbepoetin

Peritubular cells in the kidneys respond to hypoxia and synthesize and release *erythropoietin* [ee-rith-ro-POI-eh-tin; EPO], a glycoprotein. EPO stimulates stem cells to differentiate into proerythroblasts and promotes the release of reticulocytes from the marrow and initiation of hemoglobin formation. Thus, EPO

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regulates red blood cell proliferation and differentiation in bone marrow. Human *erythropoietin* (*epoetin alfa*), produced by recombinant DNA technology, is effective in the treatment of anemia caused by ESRD, human immunodeficiency virus infection, bone marrow disorders, prematurity, and malignancy. A long-acting form of *erythropoietin*, *darbepoetin* [dar-be-POE-e-tin], has a half-life about three times that of *epoetin alfa* due to the addition of two carbohydrate chains. These agents are well tolerated and are administered intravenously in renal dialysis patients or subcutaneously for other indications. Side effects such as blood pressure elevation and arthralgia may occur in some cases. [Note: The former may be due to increases in peripheral vascular resistance and/or blood viscosity.] In addition, iron supplementation may be required to ensure an adequate response.

When *epoetin alfa* is used to target hemoglobin concentrations over 11 g/dL, serious cardiovascular events (such as thrombosis and severe hypertension), increased risk of death, shortened time to tumor progression, and decreased survival have been observed. The recommendations for all patients receiving *epoetin alfa* or *darbepoetin* include a minimum effective dose that does not exceed a hemoglobin level of 12 g/dL and a hemoglobin level that does not rise by more than 1 g/dL over a 2-week period. Additionally, if the hemoglobin level exceeds 10 g/dL, doses of *epoetin alfa* or *darbepoetin* should be reduced or treatment should be discontinued. Neither agent has any value in the acute treatment of anemia due to their delayed onset of action.

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III. AGENTS USED TO TREAT NEUTROPENIA

Myeloid growth factors or granulocyte colony-stimulating factors (G-CSF), such as *filgrastim* [fil-GRAS-tim], *tbo-filgrastim*, and *pegfilgrastim* [peg-fil-GRAS-tim], and granulocyte-macrophage

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colony-stimulating factors (GM-CSF), such as *sargramostim* [sar-GRA-moe-stim], stimulate granulocyte production in the bone marrow to increase neutrophil counts and reduce the duration of severe neutropenia. These agents are typically used prophylactically to reduce the risk of neutropenia following chemotherapy and bone marrow transplantation. *Filgrastim* and *sargramostim* can be dosed either subcutaneously or intravenously, whereas *tbo-filgrastim* and *pegfilgrastim* are dosed subcutaneously only. The main difference between the available agents is in the frequency of dosing. *Filgrastim*, *tbo-filgrastim*, and *sargramostim* are dosed once a day, based on weight, beginning 24 to 72 hours after chemotherapy, until the absolute neutrophil count (ANC) reaches 5,000 to 10,000/µL. *Pegfilgrastim* is a pegylated form of G-CSF, resulting in a longer half-life when compared to the other agents, and is administered as a single fixed dose 24 hours after chemotherapy. Monitoring of ANC is typically not necessary with *pegfilgrastim.* There is no evidence to show superiority of one agent over another in terms of efficacy, safety, or tolerability. Bone pain is a common adverse effect with these agents.

IV. AGENTS USED TO TREAT SICKLE CELL DISEASE

A. Hydroxyurea

Hydroxyurea [hye-DROX-ee-yoo-ree-ah] is an oral ribonucleotide reductase inhibitor that can reduce the frequency of painful sickle cell crises (Figure 44.4). In sickle cell disease, *hydroxyurea* increases fetal hemoglobin (HbF) levels, thus diluting the abnormal hemoglobin S (HbS). Polymerization of HbS is delayed and reduced in treated patients, so that painful crises are not caused by sickled cells blocking capillaries and causing tissue anoxia. A clinical response may take 3 to 6 months. Important side effects of *hydroxyurea* include bone marrow suppression and cutaneous vasculitis. It is important that *hydroxyurea* is

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administered under the supervision of a provider experienced in the treatment of sickle cell disease. *Hydroxyurea* is also used off-label to treat acute myelogenous leukemia, psoriasis, and polycythemia vera.

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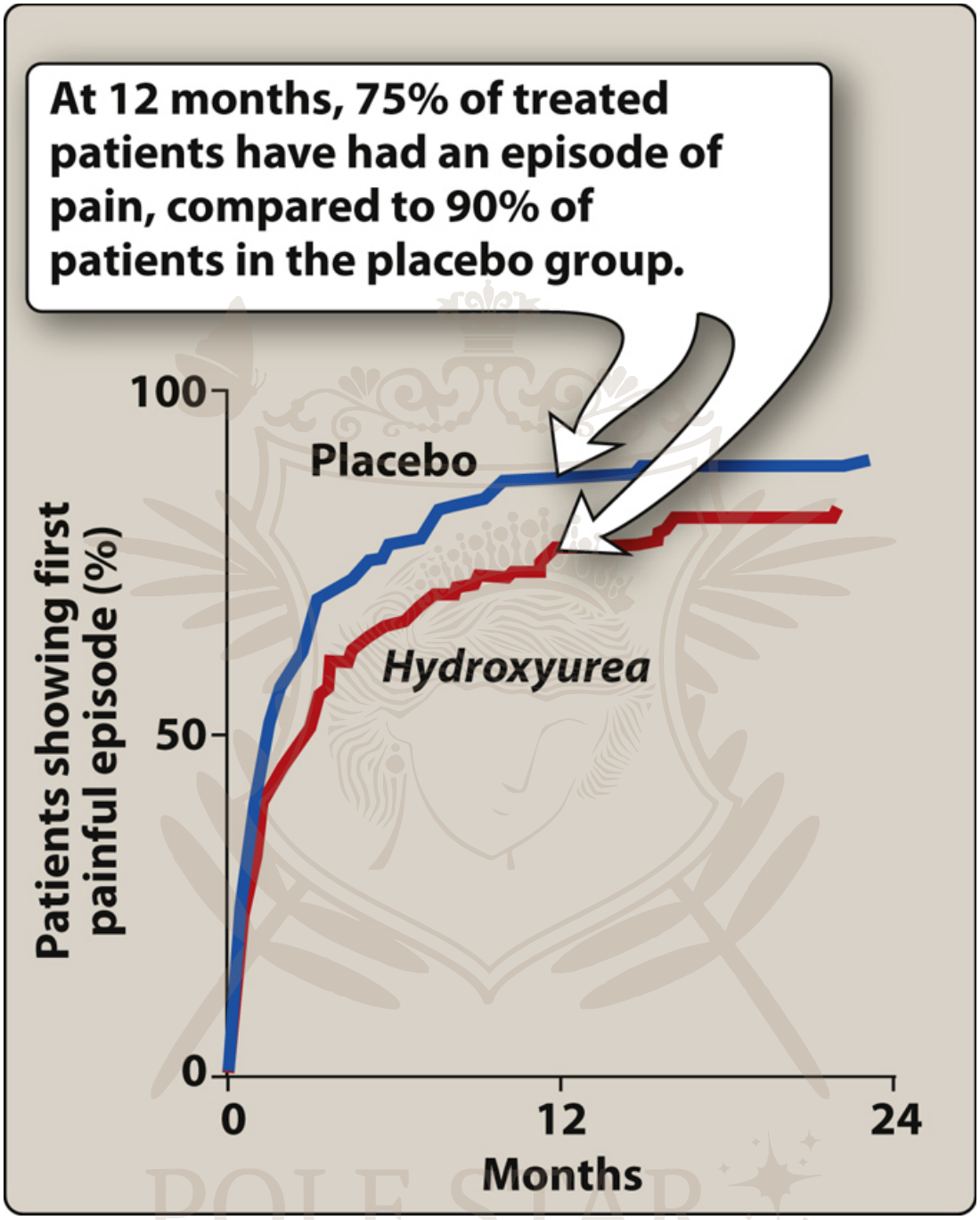

Figure 44.4 Effect of treatment with *hydroxyurea* on the percentage of sickle cell patients experiencing first painful episode.

B. Crizanlizumab

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Crizanlizumab [KRIZ-an-LIZ-ue-mab] is a humanized monoclonal antibody that binds to P-selectin and blocks interactions with its ligands. By binding to P-selectin on the surface of activated endothelial cells and platelets, *crizanlizumab* blocks interactions between endothelial cells, red blood cells, platelets, and leukocytes. By blocking these interactions, *crizanlizumab* reduces blockade of capillaries by sickled RBCs, relieving anoxia, and reducing the number of sickle cell crises. *Crizanlizumab* is indicated for patients age 16 and older with sickle cell anemia and is administered as an intravenous infusion at weeks 0 and 2 and then every 4 weeks thereafter. The most common adverse effects include infusion-related reactions, nausea, arthralgia, back pain, and pyrexia.

C. Voxelotor

Voxelotor [vox-EL-oh-tor] inhibits polymerization of HbS by binding to the alpha chain of HbS. *Voxelotor* prevents polymerization of HbS by decreasing the concentration of deoxygenated HbS, which is thought to be the form of HbS that leads to polymerization and sickling. *Voxelotor* is approved for patients 12 and older and is given as a once-daily oral dose. This drug is generally well tolerated, with headache, diarrhea, and GI upset noted as the most common side effects. *Voxelotor* is metabolized by CYP3A4, and dosage adjustments may need to be made in the presence of CYP3A4 inducers or inhibitors.

Figure 44.5 provides a summary of medications used in the management of anemia.

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MEDICATION	ADVERSE EFFECTS	DRUG INTERACTIONS	MONITORING PARAMETERS
Treatment of anemia			
Cyanocobalamin/B_{12}	Injection site pain Arthralgia Dizziness Headache Nasopharyngitis Anaphylaxis	Proton pump inhibitors—may decrease oral absorption of vitamin B_{12}	Vitamin B_{12} Folate Iron
Erythropoietin/epoetin alfa	Edema Pruritus Nausea/vomiting Hypertension CVA Thrombosis	*Darbepoetin alfa*—duplication of therapy can lead to increased adverse events	H/H Serum ferritin Blood pressure
Darbepoetin alfa	Edema Dyspnea Hypertension CVA Thrombosis	*Epoetin alfa*—duplication of therapy can lead to increased adverse events	H/H Serum ferritin Blood pressure
Folic acid	Bad taste in mouth Nausea Confusion Irritability	*Cholestyramine*—may interfere with absorption	CBC Serum folate
Iron	Pruritus N/V/D Headache Anaphylaxis	Calcium and calcium-containing antacids—decreases iron absorption *Deferoxamine*—chelates iron *Dimercaprol*—chelates iron Magnesium—decreases iron absorption *Tetracycline* and fluoroquinolone antibiotics—iron may decrease the absorption of these antibiotics	H/H Serum iron TIBC Transferrin Reticulocyte count
Treatment of sickle cell anemia			
Hydroxyurea	Myelosuppression Skin ulcer Secondary leukemia Elevated liver enzymes	HIV medications—*hydroxyurea* can decrease CD4 counts Salicylates—increase bleeding risk *Probenecid*—↑ uric acid	CBC
Crizanlizumab	Injection-related reactions Nausea Back pain Arthralgia Pyrexia	None known	CBC
Voxelotor	Headache Diarrhea Gastrointestinal upset	CYP3A4 inducers and inhibitors, such as grapefruit juice and *phenytoin*, respectively	CBC, Hepatic function

Figure 44.5 Medications for the management of anemia.CBC = complete blood count; CVA = cerebrovascular accident; H/H = hemoglobin and hematocrit; N/V/D = nausea/vomiting/diarrhea; TIBC = total iron binding capacity.

POLE STAR

Chapter Summary

- Anemia is defined as a below-normal plasma hemoglobin concentration. General signs and symptoms of anemia include fatigue, palpitations, shortness of breath, pallor, dizziness, and insomnia.

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- Anemia can be related to many conditions including blood loss, drugs, genetic predispositions, and nutritional deficiencies (iron, folic acid, vitamin B_{12}).
- Iron deficiency can occur from depletion of iron stores and/or inadequate intake and is treated with iron supplementation. Several oral and parenteral forms of iron are available. GI disturbances and dark stools are common adverse effects, and some forms of parenteral iron (*iron dextran*) can cause serious anaphylactoid reactions.
- Megaloblastic anemia results from a deficiency in vitamin B_{12} and/or folic acid. Empiric treatment should consist of a combination of *folic acid* and *vitamin* B_{12}. Patients who do not make intrinsic factor need to be treated with parenteral *vitamin* B_{12}.
- *Erythropoietin* and *darbepoetin* are used to stimulate stem cells to differentiate and promote the release of reticulocytes. These drugs are used to treat anemia caused by ESRD, human immunodeficiency virus infection, bone marrow disorders, prematurity, and malignancy.
- Myeloid growth factors or G-CSF and GM-CSF stimulate granulocyte production to reduce the duration of severe neutropenia. There is no evidence to suggest that one agent is superior to another.
- *Hydroxyurea*, a ribonucleoside reductase inhibitor, increases HgF, which reduces sickle cell crisis events in patients with sickle cell anemia. Important side effects of *hydroxyurea* include bone marrow suppression and cutaneous vasculitis.
- *Crizanlizumab* is a humanized monoclonal antibody that binds to P-selectin, reducing blockade of capillaries by sickled RBCs, relieving anoxia, and reducing the number of sickle cell crises. The most common side effects include infusion-related reactions, nausea, arthralgia, back pain, and pyrexia.

STUDY QUESTIONS

Choose the ONE best answer.

44.1 Which of the following is an appropriate treatment for a nutritional anemia that presents as a hunger for ice and/or upward curvature of the fingernails?

A. Vitamin B_{12} (cyanocobalamin)
B. Folic acid

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C. Vitamin D
D. Iron

Correct answer = D. Vitamin B_{12}, folic acid, and iron deficiencies all contribute to anemia, but iron deficiency is associated with pica (hunger for ice or dirt) and koilonychias (upward curvature of toenails/fingernails). Vitamin D deficiency does exist but does not cause anemia.

44.2 Which of the following iron supplements contains the highest percentage of elemental iron?

A. Ferrous sulfate
B. Carbonyl iron
C. Ferrous gluconate
D. Ferric ammonium citrate

Correct answer = B. Ferrous sulfate contains 20% (or 30% in the anhydrous formulation), ferrous gluconate contains 12%, and ferric ammonium citrate contains 18% of elemental iron. These are all well below the percent of elemental iron in carbonyl iron, which contains 100% elemental iron.

44.3 A 56-year-old woman is discovered to have megaloblastic anemia. Her past medical history is significant for alcoholism. Which of the following would be the best treatment option for this patient?

A. Oral vitamin B_{12}
B. Parenteral vitamin B_{12}
C. Oral folic acid
D. Oral vitamin B_{12} with oral folic acid

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Correct answer = D. The patient has a history of alcoholism, which would suggest folic acid deficiency anemia. However, folic acid administration alone reverses the hematologic abnormality and masks possible vitamin B_{12} deficiency, which can then proceed to severe neurologic dysfunction and disease. The cause of megaloblastic anemia needs to be determined in order to be specific in terms of treatment. Therefore, megaloblastic anemia should not be

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treated with folic acid alone but, rather, with a combination of folic acid and vitamin B_{12}.

44.4 A 45-year-old woman visits her physician for a follow-up visit after a trip to the emergency room, where she was diagnosed with anemia. She reports that she is taking a pill three times a day for anemia, and she is concerned because her stool seems darker. Which of the following medications is she most likely taking for anemia?

A. Ferrous gluconate
B. Folic acid
C. Iron dextran
D. Vitamin B_{12}

Correct answer = A. Any form of iron supplementation can cause dark stools. The patient was given a medication orally three times a day, which makes ferrous gluconate the best answer choice. Iron dextran is given as an infusion.

44.5 A 63-year-old woman with anemia secondary to chronic kidney disease and a hemoglobin level of 8.6 g/dL is treated with epoetin alfa. Eight days after the initial dose of epoetin alfa, the patient's hemoglobin is 10.5 g/dL. Which of the following is the most appropriate next step in the management of this patient's anemia?

A. Discontinue epoetin alfa
B. Discontinue epoetin alfa and initiate darbepoetin
C. Continue epoetin alfa
D. Increase the dose of epoetin alfa

Correct answer = A. Hemoglobin has increased to more than 10 g/dL and more than 1 g/dL in 2 weeks, so epoetin alfa should be discontinued or the dose reduced. Switching to darbepoetin, continuing epoetin alfa, or increasing the dose of epoetin alfa would continue to increase hemoglobin and lead to increased risk of cardiovascular events.

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44.6 Which of the following drugs would be beneficial to reduce the frequency of painful crises in a patient with sickle cell disease?

A. Epoetin alfa
B. Filgrastim
C. Hydroxyurea
D. Sargramostim

Correct answer = C. Clinical evidence supports the use of hydroxyurea for reducing the frequency and severity of painful sickle cell crises during the course of sickle cell disease. Epoetin alfa helps increase hemoglobin and red blood cell production in anemias secondary to chronic kidney disease, HIV, bone marrow disorders, and other disorders. Filgrastim and sargramostim stimulate granulocyte production in the marrow to increase the neutrophil counts and reduce the duration of severe neutropenia.

44.7 A 66-year-old woman is receiving chemotherapy for stage IV breast cancer. As part of her treatment regimen, she received a dose of filgrastim prophylactically to reduce her risk of neutropenia. Which of the following adverse effects is she most likely to experience as a result of filgrastim treatment?

A. Hair loss
B. Bone pain
C. Osteopenia
D. Diarrhea

Correct answer = B. Drugs that treat neutropenia, such as filgrastim, can cause bone pain as a side effect. This side effect is not specific to filgrastim and can be observed for pegfilgrastim and sargramostim.

44.8 A patient has been taking ferrous sulfate 325 mg twice daily for 2 weeks and is complaining of a bad taste after each dose. Which of the following once-daily, oral iron formulations would improve tolerability and provide a similar total daily dose of elemental iron as twice-daily ferrous sulfate?

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A. Ferric ammonium citrate 25 mg
B. Ferrous gluconate 100 mg
C. Ferrous sulfate, anhydrous 142 mg
D. Polysaccharide–iron complex 150 mg

Correct answer = D. Once-daily polysaccharide–iron complex (150 mg = 150 mg elemental iron) is tasteless and odorless, with a similar total daily dose of elemental iron as ferrous sulfate 325 mg twice daily (130 mg elemental iron/day). Once-daily ferric ammonium citrate 25 mg (4.5 mg elemental iron) is less bioavailable than twice-daily ferrous sulfate. Ferrous sulfate and ferrous gluconate have similar tolerability, but once-daily ferrous gluconate has less elemental iron (12 mg elemental iron). Ferrous sulfate, anhydrous has better tolerability with the extended-release formulation, but has less elemental iron (43 mg elemental iron) administered once daily compared to twice-daily ferrous sulfate.

44.9 A 20-year-old woman is currently being treated with aggressive chemotherapy for ovarian carcinoma. She presents with severe fatigue and is diagnosed with significant iron deficiency anemia. Therapy with iron dextran is recommended. Which of the following is the most appropriate to recommend prior to initiation of this therapy?

A. Recheck hemoglobin levels
B. Give a test dose
C. Pretreat with antinausea medication
D. Start a blood transfusion

Correct answer = B. Rarely, iron dextran can cause fatal hypersensitivity and anaphylactoid reactions. To avoid this, a test dose should be administered prior to initiating iron dextran therapy.

44.10 An 81-year-old woman presents to the emergency department with progressive weakness, fatigue, confusion, and reports of seeing people in her house who were trying to hurt her but who were not physically present. Her physical examination was positive for pallor but negative for koilonychias

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or cracking at the corners of the mouth. Which of the following deficiencies would be the highest priority in this patient's workup?

A. Vitamin B_{12}
B. Iron
C. Folate
D. Calcium

Correct answer = A. Based on the presentation of confusion and hallucinations, vitamin B_{12} deficiency should be considered the highest priority. Second priority would be to assess folate deficiency, since symptoms are similar to vitamin B_{12} deficiency. Iron would be the third priority due to the patient's age, even without the presence of koilonychias or cracking of the mouth. Last priority would be to assess age-related deficiencies in calcium, which could lead to fatigue as well as muscle cramps, poor appetite, and abnormal heart rhythms.

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45

Drugs for Dermatologic Disorders

Stacey D. Curtis, William Cary Mobley

I. OVERVIEW

The skin is a complex and dynamic organ comprised of cells, tissues, and biomolecules that coordinate to provide many interdependent functions. Skin provides protection from environmental insults from noxious chemicals, infectious pathogens, and ultraviolet radiation, as well as serving vital functions in wound repair, sensation, thermoregulation, and vitamin D synthesis. This chapter focuses on drugs that are used for some of the more common skin conditions, including psoriasis, acne, rosacea, infections, pigmentation disorders, and alopecia. Drugs for acne, superficial bacterial infections, and rosacea are summarized in Figure 45.1. [Note: Agents for fungal infections of the skin are covered in the chapter on antifungals (see Chapter 33).]

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AGENTS FOR ACNE

Adapalene DIFFERIN
Azelaic acid AZELEX
Benzoyl peroxide VARIOUS
Clindamycin CLEOCIN
Dapsone ACZONE
Doxycycline DORYX
Erythromycin VARIOUS
Isotretinoin VARIOUS
Minocycline (oral) VARIOUS
Minocycline (topical) AMZEEQ
Salicylic acid VARIOUS
Sarecycline SEYSARA
Tazarotene TAZORAC
Tretinoin RETIN-A

AGENTS FOR SUPERFICIAL BACTERIAL INFECTIONS

Bacitracin VARIOUS
Gentamicin VARIOUS
Mupirocin GENERIC ONLY
Neomycin VARIOUS
Ozenoxacin XEPI
Polymyxin VARIOUS
Retapamulin ALTABAX

AGENTS USED FOR ROSACEA

Azelaic acid FINACEA
Brimonidine MIRVASO
Doxycycline ORACEA
Metronidazole METROGEL
Minocycline ZILXI
Oxymetazoline RHOFADE
Sulfacetamide sodium VARIOUS

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Figure 45.1 Summary of drugs for acne, superficial bacterial infections, and rosacea.

II. TOPICAL PREPARATIONS

The skin is composed of two main layers, the epidermis and the dermis (Figure 45.2). The epidermis is composed of several layers of keratinocytes, with the outermost layer, the stratum corneum, serving as the primary barrier to external insults. The dermis, located between the epidermis and the subcutaneous tissue, is composed of connective tissue and contains many specialized structures, such as sweat glands, sebaceous glands, hair follicles, and blood vessels. Defects in skin structure and function induced by genetics and by environmental insults can lead to numerous dermatological conditions, many of which can be controlled or cured with the use of drug therapy.

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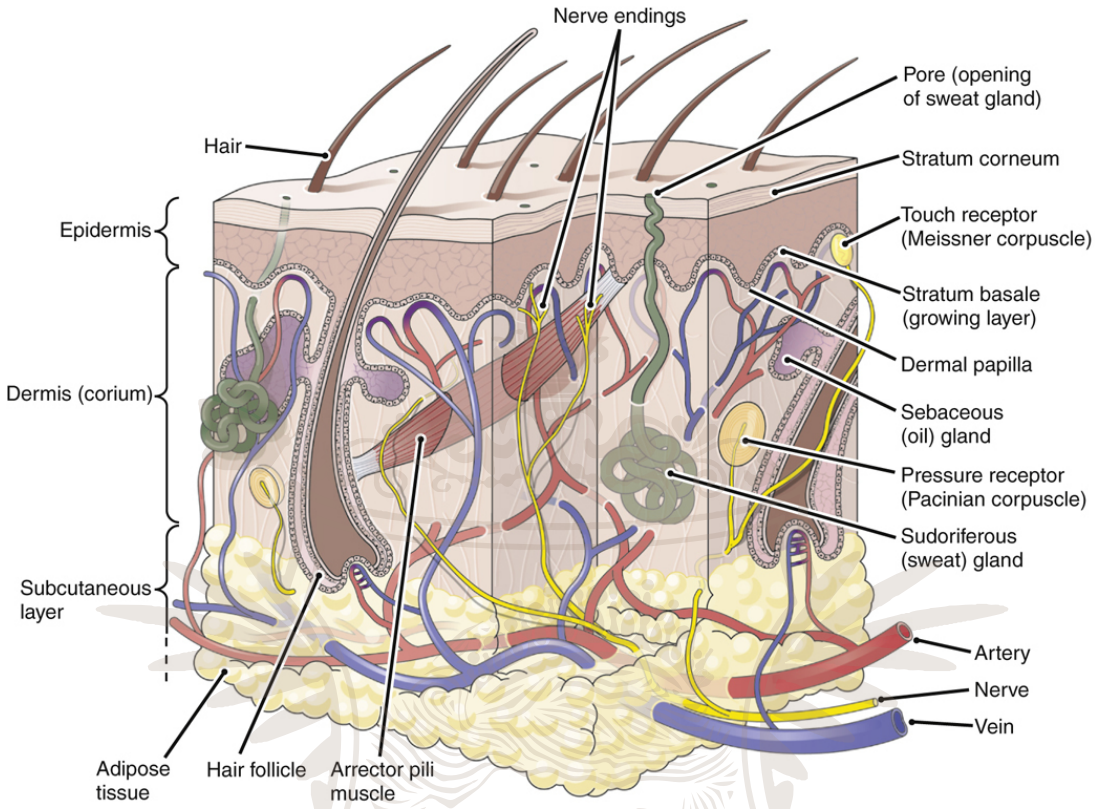

Figure 45.2 Cross section of the skin.

Use of topical agents for treatment of dermatologic disorders is not only convenient but also can minimize systemic adverse effects. Common topical dosage forms include sprays, powders, lotions, creams, pastes, gels, ointments, and foams. The choice of dosage form for a particular condition involves factors such as occlusiveness, ease of application, patient acceptance, and drug potency. The choice also includes consideration of the thickness and integrity of the stratum corneum, as well as the type, location, and extent of the lesions being treated.

III. AGENTS FOR ACNE

Acne vulgaris (common acne) is a common skin disorder that occurs in about 85% of individuals 12 to 24 years of age, coinciding with an increase in androgen production. [Note: Use of oral contraceptives

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may help decrease circulating levels of free androgen and reduce symptoms of acne in females (see Chapter 25).] Formation of acne lesions begins with excessive proliferation and adhesion of skin cells that form a keratin plug (microcomedone), which closes the hair follicle (Figure 45.3). Within the closed hair follicle, skin cells are shed and sebum production continues. This causes the follicle to dilate to form a comedone.

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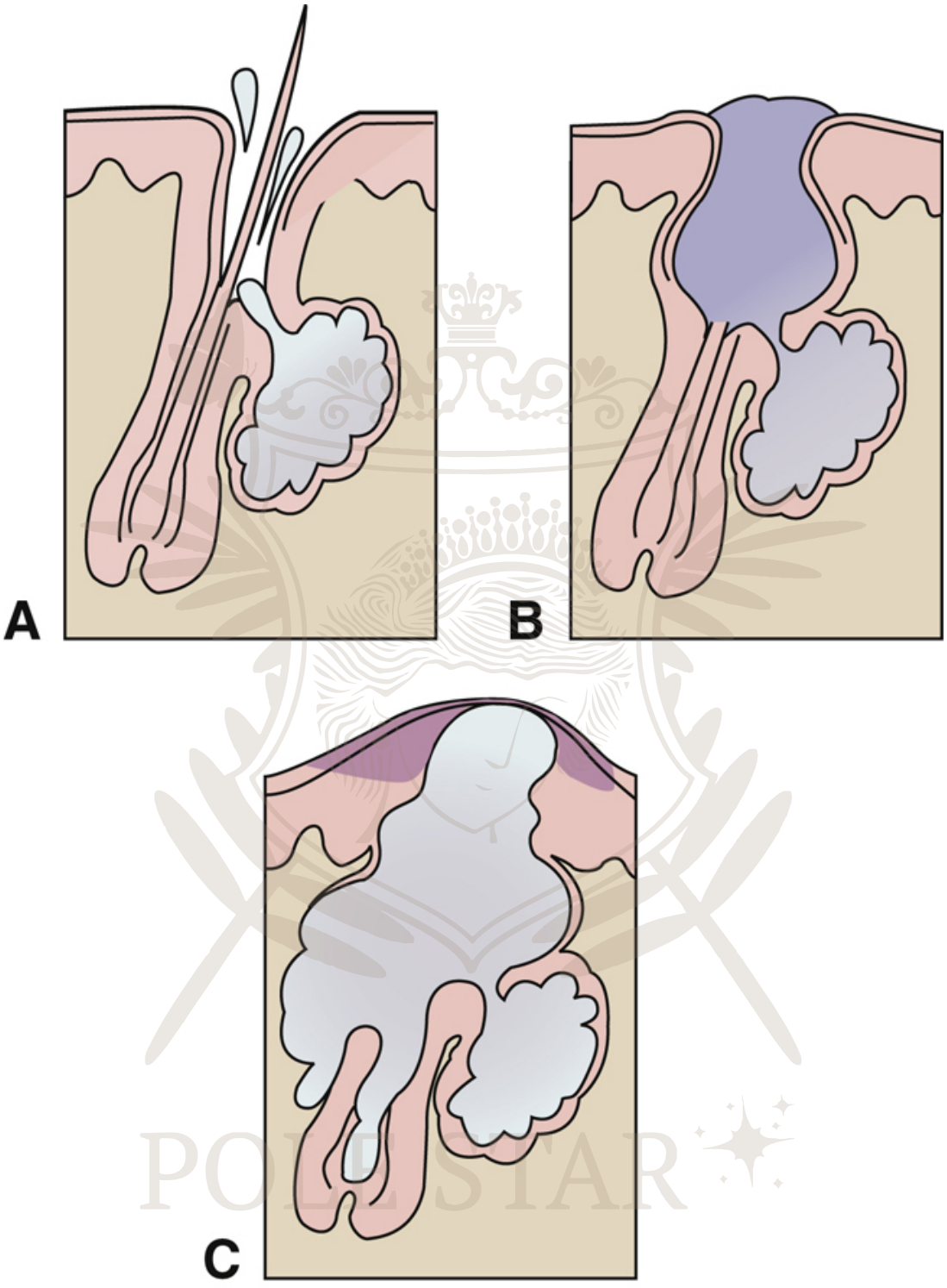

Figure 45.3 Acne vulgaris.A, Normal sebaceous gland and hair follicle. B, Comedone formation. C, Pustule formation.

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The sebum serves as a nutrient for the proliferation of Cutibacterium acnes, which along with other factors triggers an inflammatory response that causes the formation of a pustule or papule—the pimple. If this progresses, the follicular wall can rupture, leading to the formation of an inflamed nodule. Different medications can be used alone or in combination to affect one or more of these pathological components and clear the acne lesions.

A. Antibiotics

Topical and oral antibiotics are frequently used in acne, with oral antibiotics reserved for moderate to severe acne. The use of antibiotics in acne is based not only on their antibacterial effects but also on anti-inflammatory properties, which can be significant for some classes of antibiotics, such as the tetracyclines.

The most common topical antibiotics used in the treatment of acne are *clindamycin* [klin-da-MYE-sin] (solution or gel) and *erythromycin* [er-ITH-roe-MYE-sin] (cream, gel, or lotion). *Minocycline* [mi-no-SYE-kleen], a tetracycline antibiotic, is also available as a topical foam. Topical antibiotics are associated with significantly less systemic exposure than oral antibiotics, and topical forms tend to be well tolerated. Adverse effects include local irritation and burning, erythema, and dryness.

Oral antibiotics frequently used for acne are the tetracyclines *doxycycline* [DOX-i-SYE-kleen] and *minocycline. Sarecycline* [SAR-e-SYE-kleen] is a newer member of the tetracycline family, and it is approved for the treatment of moderate to severe acne. Compared to other tetracyclines, it has a narrower antimicrobial spectrum, which may result in reduced disruption of gastrointestinal microflora and a reduced potential for developing resistance. It is used less often than other tetracyclines due to cost considerations. Adverse effects of oral tetracyclines include gastrointestinal disturbances and photosensitivity. Oral macrolide antibiotics such as *erythromycin* and *azithromycin* [a-ZITH-roe-MYE-sin] are alternatives for the management of moderate to

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severe acne in patients who have a contraindication to tetracyclines (for example, pregnancy).

The most significant concern with use of both topical and oral antibiotics in the treatment of acne is the development of bacterial resistance. Measures to limit the development of resistance include using antibiotics only in combination with other acne agents, using oral antibiotics for the shortest time possible, and using low-dose oral antibiotics (subantimicrobial dosing) when possible. Also, once acne lesions are clear, patients should discontinue antibiotics and begin maintenance therapy with other effective topical agents, such as *benzoyl peroxide* or retinoids. Antibiotics are covered in more detail in the chapters on anti-infective therapy (see Chapter 30).

B. Azelaic acid

Azelaic [aze-eh-LAY-ik] *acid* is a naturally occurring dicarboxylic acid that has antibacterial activity against C. acnes through its ability to inhibit protein synthesis. It also exhibits anti-inflammatory activity, inhibits the division and differentiation of keratinocytes, and shows comedolytic activity. *Azelaic acid* exhibits a lightening effect on hyperpigmented skin, which makes it useful for patients who experience dyspigmentation as a consequence of inflammatory acne. It is available as a cream and a gel, and the major adverse effects are mild and transient pruritus, burning, stinging, and tingling.

C. Benzoyl peroxide

Benzoyl peroxide [BEN-zoyl per-OX-ide] is a commonly used topical medication that improves acne primarily through its bactericidal action, where its oxidizing activity is lethal for *C. acnes.* It shows no bacterial resistance. The agent also reduces inflammation and has comedolytic activity. *Benzoyl peroxide* is available in topical washes, foams, creams, and gels. The major adverse effects are dry skin, irritation, and bleaching of bedding

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and clothing. It may also cause contact dermatitis in some patients.

D. Dapsone

Dapsone [DAP-sone] is a sulfone that exhibits both anti-inflammatory and antibacterial activity and is effective at reducing inflammatory acne lesion counts. It may also provide some reduction in noninflammatory lesions, as well. The anti-inflammatory activity derives partly from its ability to interfere with neutrophilic function and to reduce the production of tumor necrosis factor-α (TNF-α) by mononuclear cells. *Dapsone* is available as a topical gel. Adverse effects may consist of transient oiliness, dryness, and erythema, which may be at least in part due to the nondrug part of the formulation.

E. Retinoids

Retinoids are vitamin A derivatives that interact with retinoid receptors to regulate gene expression in a manner that normalizes keratinocyte differentiation and reduces hyperproliferation (giving them comedolytic activity). They also reduce sebum production and inflammation. These diverse effects make retinoids useful for acne, as well as a variety of other conditions, including psoriasis and severe rosacea. For acne vulgaris, the topical retinoids *tretinoin* [TRET-i-no-in], *adapalene* [a-DAP-a-leen], and *tazarotene* [ta-ZAR-oh-teen] are used for mild and moderate forms, whereas the oral retinoid *isotretinoin* [eye-so-TRET-i-no-in] is reserved for severe nodular forms of acne.

Adverse effects of the topical retinoids include erythema, desquamation, burning, and stinging. These effects often decrease with time. Other potential adverse effects include dry mucous membranes and photosensitivity. Patients should be cautioned to wear sunscreen. Though systemic absorption from topical formulations is generally limited, use should be avoided during pregnancy, particularly for topical *tazarotene* which is the most teratogenic of the topical retinoids for acne. Oral *isotretinoin*,

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used in severe acne, has potentially serious adverse effects including psychiatric effects and birth defects. It is contraindicated in women who are pregnant or intend to become pregnant.

F. Salicylic acid

Topical *salicylic* [sal-i-SIL-ik] *acid*, a β-hydroxy acid, penetrates the pilosebaceous unit and works as an exfoliant to clear comedones. Its comedolytic effects are not as pronounced as those of the retinoids. The drug has mild anti-inflammatory activity and is keratolytic at higher concentrations. *Salicylic acid* is used as a treatment for mild acne and is available in many over-the-counter facial washes and medicated treatment pads. Mild skin peeling, dryness, and local irritation are adverse effects.

G. Sulfacetamide sodium

Sulfacetamide sodium [SUL-fa-SET-a-mide SOE-dee-um] interferes with bacterial growth and is often combined with sulfur, a keratolytic agent. The combination is used to treat inflammatory acne lesions when present. The product is available as a cleanser, cream, foam, gel, lotion, pads, suspension, and a wash. The most common adverse effects include contact dermatitis, erythema, pruritus, and xeroderma.

Clinical Application 45.1 Treatment of Acne

Topical therapy is the standard of care for mild to moderate acne. However, patients with moderate to severe acne usually require systemic therapy. Combination therapy targeting the four pathogenic mechanisms is recommended, as it is often more effective than monotherapy, can reduce side effects, and may minimize resistance or tolerance to individual treatments. The general strategy for combination therapy is to use the least number of agents at the lowest possible dosages to ensure efficacy, safety, avoidance of resistance, and to maximize patient adherence. To reduce development of new lesions, topical agents require application to the whole affected area, and given that it takes about 8 weeks for a microcomedone to mature, acne therapy must be continued beyond this duration to fully assess efficacy of the regimen. Additionally, as microcomedones can rebound almost immediately after therapy is discontinued, some form of acne therapy may need to continue for months or

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years. Thus, it is important to continue to support and encourage patients so that they remain adherent to lengthy regimens that address current lesions and prevent future lesions.

IV. AGENTS FOR SUPERFICIAL BACTERIAL INFECTIONS

Several gram-positive and gram-negative bacteria can cause various superficial skin infections, such as folliculitis and impetigo, as well as deeper infections, such as erysipelas and cellulitis. In more severe cases, skin infections can lead to ulceration and systemic infections. This section covers topical antibacterial agents that can be used for the treatment and prevention of certain superficial skin infections.

A. Bacitracin

Bacitracin [bas-i-TRAY-sin] is a peptide antibiotic active against many gram-positive organisms. It is used mainly in topical formulations; if used systemically, it is toxic. It is frequently found in combination products with *neomycin* and/or *polymyxin* (see below). *Bacitracin*, when used in combination with *polymyxin*, is mostly used for the prevention of skin infections after burns or minor scrapes. It is available as an ointment.

B. Gentamicin

Gentamicin [GEN-ta-MYE-sin] is an aminoglycoside antibiotic that interferes with bacterial protein synthesis targeting gram-negative organisms. This agent is often used in combination with other agents to treat skin infections caused by gram-negative organisms. It is available as a cream and an ointment. Topical use of this agent rarely causes systemic side effects.

C. Mupirocin

Mupirocin [mue-PIR-oh-sin] is an antibiotic that works by inhibiting protein synthesis targeting gram-positive organisms. It is useful in

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treating impetigo (a contagious skin infection caused by streptococci or staphylococci; Figure 45.4) and other serious gram-positive skin infections, including infections caused by *methicillin*-resistant Staphylococcus aureus (MRSA). It is available as a cream and an ointment. [Note: Intranasal *mupirocin* may be used to eradicate colonization with MRSA and reduce the risk of infection in hospitalized patients.] The most common adverse effects are pruritus, skin rash, and burning.

Figure 45.4 Impetigo on the face.

D. Neomycin

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Neomycin [nee-oh-MY-sin] is an antibiotic that interferes with bacterial protein synthesis and is active primarily against gram-negative organisms, with some activity against gram-positive organisms. This agent is often formulated with other topical anti-infectives, such as *bacitracin* and *polymyxin* to treat skin infections. The combination is available as an ointment. Common adverse effects associated with the combination agents include contact dermatitis, erythema, rash, and urticaria.

E. Ozenoxacin

Ozenoxacin [oz-en-OX-a-sin] is a topical quinolone antibiotic that inhibits the bacterial DNA replication enzymes DNA gyrase A and topoisomerase IV. It has bactericidal activity against staphylococci and streptococci and has demonstrated activity against MRSA isolates. *Ozenoxacin* is used in the treatment of impetigo in adults and children 2 months of age and older. Possible adverse effects include itching, skin redness, and skin dryness.

F. Polymyxin

Polymyxin [paw-lee-MIX-in] *B* is a cyclic hydrophobic peptide that disrupts the bacterial cell membrane of gram-negative organisms. As noted earlier, it is commonly combined with *bacitracin* (“double antibiotic”) and *neomycin* with *bacitracin* (“triple antibiotic”) in topical products used for the prevention of skin infections after minor skin trauma. These combinations are available as ointments.

G. Retapamulin

Retapamulin [RE-te-PAM-ue-lin] is a protein synthesis inhibitor active against gram-positive organisms. It is indicated for the treatment of impetigo. The only available dosage form is an ointment, and the most common adverse effects are pruritus and skin irritation.

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V. AGENTS USED FOR ROSACEA

Rosacea is a common inflammatory disorder affecting the central portion of facial skin including the cheeks, chin, forehead, and nose. Common clinical features include facial erythema (flushing) and inflammatory lesions that are similar to acne lesions. The signs, symptoms, and severity determine the treatment for this disorder. *Azelaic acid* is one potential treatment for rosacea. Other topical and oral products for rosacea are described below.

A. Brimonidine

Brimonidine [bri-MOE-ni-deen] is an α_2 adrenoceptor agonist used for erythematotelangiectatic rosacea (ETR). It reduces erythema through vasoconstriction. It is available as a gel and its major adverse effects are burning, localized warm feeling, and flushing. [Note: *Brimonidine* ophthalmic solution is used for the treatment of glaucoma.]

B. Doxycycline

Doxycycline is a tetracycline antibacterial agent used orally at low doses, where it exerts its effects on rosacea through its anti-inflammatory effects, rather than antimicrobial actions. It is available as a capsule and tablet, and its major adverse effects include diarrhea, nausea, dyspepsia, and nasopharyngitis.

C. Ivermectin

Ivermectin [eye-ver-MEK-tin] is an antiparasitic agent and its mechanism of action is unknown in the treatment of papulopustular rosacea (PPR). However, it appears to have both an anti-inflammatory effect on the skin and a lethal effect on *Demodex* mites, a skin mite that is associated with rosacea. *Ivermectin* is available as a once-daily cream. It is well tolerated with the possibility of skin irritation and burning.

D. Metronidazole

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Metronidazole [me-troe-NI-da-zole] is an antibacterial agent used topically for PPR. It is believed to work in rosacea through anti-inflammatory or immunosuppressive effects, rather than through its antibacterial effects. It is available as a cream, gel, and lotion, and its major adverse effects are burning, erythema, skin irritation, xeroderma, and acne vulgaris.

E. Minocycline

Topical *minocycline* foam is used for the treatment of PPR. The lipophilic foam enables the local anti-inflammatory effects of minocycline while reducing the risk of systemic adverse effects (see acne section above).

F. Oxymetazoline

Oxymetazoline [ox-e-meh-TAZ-oh-leen] is an α_1 adrenoceptor agonist used for ETR. It reduces erythema through vasoconstriction. *Oxymetazoline* is available as a cream, and its major adverse effects are application site dermatitis, worsening inflammatory lesions, pruritus, erythema, and a burning sensation.

Clinical Application 45.2 Treatment for Rosacea

Rosacea has several subtypes, and knowing the subtype can help in the selection of therapy. One type is ETR, which is characterized by facial erythema, flushing, and telangiectasia (dilation of tiny blood vessels near the surface of the skin). Another type is PPR, which is characterized by facial pustules similar to acne, and sometimes plaques (palpable, typically raised lesions >1 cm in diameter). For ETR, general skin care, including gentle cleansers and the use of moisturizers and sunscreens, along with trigger avoidance may be an adequate therapeutic approach. For moderate to severe cases, one of the topical alpha-adrenergic receptor agonists (*oxymetazoline* or *brimonidine*) can be effective in reducing erythema. These agents are usually applied to the entire face in the morning. For PPR, along with general skin care, topical agents and systemic antibiotics are mainstays in therapy. For PPR flares, short courses (for example, 4-6 weeks) of systemic antibiotics can be effective. Therapy then continues with topical agents (*metronidazole*, *ivermectin*, *azelaic acid*, or *minocycline*) for maintenance treatment.

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VI. AGENTS FOR PIGMENTATION DISORDERS

The color of skin is derived from melanin produced by melanocytes in the basal layer of the epidermis. When the melanocytes are damaged, the melanin levels are affected, which ultimately leads to pigmentation disorders. If the body does not make enough melanin, the skin gets lighter (hypopigmentation). If the body makes too much melanin, the skin gets darker (hyperpigmentation). Pigmentation disorders can be widespread and affect many areas of the skin or they can be localized. Agents used for pigmentation disorders are discussed below and summarized in Figure 45.5.

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AGENTS FOR PIGMENTATION DISORDERS

Hydroquinone GENERIC ONLY
Methoxsalen GENERIC ONLY
Tazarotene AVAGE

AGENTS FOR PSORIASIS

Acitretin SORIATANE
Adalimumab HUMIRA
Apremilast OTEZLA
Brodalumab SILIQ
Calcipotriene DOVONEX
Calcitriol VECTICAL
Certolizumab pegol CIMZIA
Coal tar VARIOUS
Etanercept ENBREL
Golimumab SIMPONI
Guselkumab TREMFYA
Infliximab REMICADE
Ixekizumab TALTZ
Methotrexate VARIOUS
Salicylic acid VARIOUS
Secukinumab COSENTYX
Tazarotene TAZORAC
Ustekinumab STELARA

AGENTS FOR ALOPECIA

Finasteride PROPECIA
Minoxidil ROGAINE

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Figure 45.5 Summary of drugs for pigmentation disorders, psoriasis, and alopecia.

A. Hydroquinone

Hydroquinone [HYE-droe-KWIN-one] is a topical skin-whitening agent that reduces hyperpigmentation associated with freckles and melasma (brown to gray-brown patches on the skin; Figure 45.6). It is often used in combination with topical retinoids to treat the signs of photoaging. The mechanism of action of *hydroquinone* is through inhibition of the tyrosinase, an enzyme required for melanin synthesis. *Hydroquinone* lightens the skin temporarily and is commonly used as a 4% preparation. It should not be used in higher concentrations, or in excessive quantities for an extended duration, as it is associated with possible carcinogenicity. The most common adverse effect is local skin irritation.

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Figure 45.6 Melasma on the face.Reprinted from S.Jensen . *Pocket Guide for Nursing Health Assessment*: A Best Practice Approach, 2nd ed. Philadelphia, PA, Wolters Kluwer (2015), with permission.

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B. Methoxsalen

Methoxsalen [meth-OX-a-len] is an oral psoralen photoactive agent that stimulates melanocytes and is used as a repigmentation agent for patients with vitiligo (Figure 45.7). It must

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be photoactivated by UV radiation to form a DNA adduct inhibiting DNA replication by a method called PUVA (psoralen plus UVA radiation). *Methoxsalen* inhibits cell proliferation and promotes cell differentiation of epithelial cells. Because of the possibilities for aging of the skin and carcinogenicity, it is used with caution. [Note: Topical corticosteroids and topical calicineurin inhibitors (for example, *tacrolimus*) are also used in the treatment of vitiligo.]

Figure 45.7 The palm is frequently affected by vitiligo.

POLE STAR

C. Tazarotene

Tazarotene is a topical retinoid, which decreases hyperpigmentation, and is sometimes used to treat the signs of photoaging. It is available as a cream, foam, and gel. The most

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common adverse effects include itching, burning, erythema, rash, and dryness.

VII. AGENTS FOR PSORIASIS

Psoriasis is a chronic autoimmune skin disease that manifests as epidermal hyperplasia and dermal inflammation, which can range from mild to disabling. It is a condition that has significant genetic associations and it tends to wax and wane, with flare-ups that can be triggered by a number of environmental factors including stress and skin trauma. There are several forms of psoriasis, with the most common form being plaque psoriasis. Plaque psoriasis is characterized by the presence of sharply demarcated, thick, erythematous plaques that are usually covered by dry silvery-white scales (Figure 45.8). The plaques range in size from 1 square centimeter to several square centimeters. In mild to moderate cases, these plaques cover less than 5% of the body surface area, but in more severe cases, they can cover more than 20% of the body. Therapies may target inflammation and the abnormal immune response, as well as epidermal hyperproliferation.

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Figure 45.8 Psoriasis.A large, scaly, erythematous plaque.

POLE STAR

A. Apremilast

Apremilast [a-PRE-mi-last] is an oral agent approved for moderate to severe plaque psoriasis. It works by inhibiting phosphodiesterase-4, which ultimately leads to reduced production of several inflammatory mediators in psoriasis. The most common adverse effects are diarrhea, nausea, and

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headache. Depression may also occur. Strong CYP450 inducers (for example, *carbamazepine*, *phenytoin*) may reduce the efficacy of *apremilast*, and coadministration is not recommended.

B. Biologic agents

Biologics are agents isolated from natural sources, including humans, animals, and microorganisms. They can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances. The biologics approved for psoriasis are all injectable, antibody-based proteins produced by recombinant DNA technology, and these agents are used for moderate to severe psoriasis. The mechanism of action results from their interaction with specific cytokines that induce or mediate T cell effector function, which is important in autoimmune diseases such as psoriasis. For example, several biologics target TNF-α, which plays multiple roles in psoriasis pathogenesis, including the stimulation of keratinocyte proliferation, neutrophils, and the release of proinflammatory cytokines. The TNF-α blockers include *etanercept* [ee-TAN-er-sept], *infliximab* [in-FLIKS-e-mab], *adalimumab* [a-da-LIM-yoo-mab], *certolizumab pegol* [ser-toe-LIZ-oo-mab PEG-ol], and *golimumab* [goe-LIM-ue-mab]. Biologics that target other cytokines important in the pathogenesis of psoriasis include the anti–IL-12/IL-23 medication, *ustekinumab* [YOO-sti-KIN-ue-mab]; the anti–IL-23 medications, *guselkumab* [gue-sel-KOO-mab] and *risankizumab* [RIS-an KIZ-ue mab]; and the anti–IL-17A medications, *secukinumab* [SEK-ue-KIN-ue-mab], *ixekizumab* [IX-ee-KIZ-ue-mab], and *brodalumab* [broe-DAL-ue-mab]. Though each agent has specific potential risks and adverse effects, shared adverse effects include injection or infusion reactions and increased risk of infections due to suppression of the immune system. In addition, because they are foreign proteins, there is a risk for the development of antidrug antibodies, which may affect efficacy over the course of therapy.

C. Keratolytic agents

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Keratolytic agents such as *coal tar* and *salicylic acid* are effective in localized psoriasis, especially on the scalp. They improve corticosteroid penetration. *Coal tar* inhibits excessive skin cell proliferation and may also have anti-inflammatory effects. Because it is cosmetically unappealing, *coal tar* may have a low acceptance rate among patients and, consequently, its use has been largely supplanted by the newer topical agents.

D. Methotrexate

Methotrexate [meth-oh-TREX-ate] is among the most commonly used systemic agents for psoriasis. The drug is used in more severe forms of psoriasis and the primary mechanism of action is immunosuppressive activity, resulting from its ability to reduce DNA synthesis in cells of the immune system, particularly T lymphocytes. *Methotrexate* is available in oral and injectable dosage forms. Among the common potential adverse effects are nausea, diarrhea, mouth ulcers, hair loss, and skin rashes. The primary long-term risk is the potential for liver damage, and therefore, periodic liver function tests are required for patients using *methotrexate*.

E. Retinoids

Retinoids normalize keratinocyte differentiation and reduce hyperproliferation and inflammation. *Tazarotene* is a topical retinoid used for the treatment of plaque psoriasis. Adverse effects are similar to other topical retinoids described for acne. *Acitretin* [a-si-TRE-tin] is a second-generation retinoid used orally in the treatment of pustular forms of psoriasis. Similar to oral *isotretinoin* used in acne, *acitretin* is teratogenic and women must avoid pregnancy for at least 3 years after use of the drug (due to its long duration of teratogenic potential). Ethanol is contraindicated with this agent. Cheilitis, pruritus, peeling skin, and hyperlipidemia are common adverse effects.

F. Topical corticosteroids

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Topical corticosteroids are a mainstay of psoriasis therapy and are used in many other skin conditions as well. The available agents differ in potencies and are formulated in a variety of dosage forms, including solutions, lotions, creams, ointments, gels, and shampoo (Figure 45.9). Upon binding to intracellular corticosteroid receptors, these agents produce numerous effects that can be beneficial for psoriasis, including anti-inflammatory, antiproliferative, immunosuppressive, and vasoconstrictive effects. Potential adverse effects, especially with the long-term use of potent corticosteroids, include skin atrophy, striae, acneiform eruptions, dermatitis, local infections, and hypopigmentation. In children, excessive use of potent agents applied to a large surface area can cause systemic adverse effects, including possible depression of the hypothalamic–pituitary–adrenal axis and growth retardation.

LOW POTENCY	INTERMEDIATE POTENCY	HIGH POTENCY	VERY HIGH POTENCY
Alclometasone dipropionate 0.05% (c, o)	Betamethasone dipropionate 0.05% (c)	Amcinonide 0.1% (c, l, o)	Betamethasone dipropionate, augmented 0.05% (o, g)
Fluocinolone acetonide 0.01% solution (s)	Clocortolone pivalate 0.1% (c)	Betamethasone dipropionate, augmented 0.05% (c, l)	Clobetasol propionate 0.05% (c, g, o)
Hydrocortisone base or acetate 0.25% to 2.5% (o, c)	Desonide 0.05% (c, l, o)	Desoximetasone 0.25% (c)	Fluocinonide 0.1% (c)
Triamcinolone acetonide 0.025% (c, l, o)	Desoximetasone 0.05% (c)	Desoximetasone 0.05% (g)	Flurandrenolide 0.05% (l)
	Fluocinolone acetonide 0.025% (c, o)	Diflorasone diacetate 0.05% (o, c)	Halobetasol propionate 0.05% (c, o)
	Flurandrenolide 0.025 to 0.5% (c, o)	Fluocinonide 0.05% (c, g, o, s)	
	Fluticasone propionate 0.005% to 0.05% (o, c)	Halcinonide 0.1% (c, o)	
	Hydrocortisone butyrate 0.1% (c, o, s)	Triamcinolone acetonide 0.5% (c, o)	
	Hydrocortisone valerate 0.2% (c, o)		
	Mometasone furoate 0.1% (c, o, l)		
	Triamcinolone acetonide 0.1% to 0.2% (c, o)		

Figure 45.9 Potency of various topical corticosteroids.c = cream; g = gel; o = ointment; s = solution.

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G. Vitamin D analogs

Calcipotriene [kal-sih-poh-TRY-een] and *calcitriol* [kal-si-TRYE-ol] are synthetic vitamin D_3 derivatives used topically to treat plaque psoriasis. They inhibit keratinocyte proliferation, enhance keratinocyte differentiation, and inhibit inflammation. *Calcipotriene* is available in cream, ointment, solution, and foam formulations, and *calcitriol* is available as an ointment. Potential adverse effects include itching, dryness, burning, irritation, and erythema.

Clinical Application 45.3 Therapy for Psoriasis

Plaque psoriasis can cause significant social morbidity, with patients potentially experiencing problems with work, activities of daily living, and socialization. Additionally, patients may feel unattractive and become depressed. Consequently, overall quality of life can suffer. Accordingly, in addition to a reduction or elimination of plaques and scales, and a reduction in flare-ups as important therapeutic outcomes, so is an improvement in quality-of-life scores. Among the therapeutic strategies for psoriasis care are monotherapy (which can limit side effects and improve adherence), combination therapy (which can often be more effective and allow for lower dosing than monotherapy), and sequential therapy (where stronger and sometimes more toxic agents are used initially to rapidly clear the lesions, followed by less toxic agents for maintenance therapy). In addition to pharmacotherapy, nonpharmacologic approaches are valuable adjuncts to psoriasis care. These include managing lifestyle factors that may trigger exacerbations (for example, stress, smoking, obesity); limiting alcohol consumption; and minimizing potential triggers to lesion formation (scratching, piercings, tattoos, sunburn, chemical irritants). Additionally, gentle cleansing, moisturization, sun protection, diet control, and engaging in physical activity can be valuable nonpharmacologic approaches for psoriasis care.

POLE STAR

VIII. AGENTS FOR ALOPECIA

Alopecia (baldness) is the partial or complete loss of hair from areas where hair normally grows. The most common type of hair loss is androgenic alopecia (also known as male pattern baldness), which can occur in men or women. Trichogenic agents are used to stimulate hair growth and slow the progression of hair loss.

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A. Finasteride

Finasteride [fih-NAH-steh-ride] is an oral 5α-reductase inhibitor that blocks conversion of testosterone to the potent androgen 5α-dihydrotestosterone (DHT). High levels of DHT can cause the hair follicle to miniaturize and atrophy. *Finasteride* decreases scalp and serum DHT concentrations, thus inhibiting a key factor in the etiology of androgenic alopecia. [Note: *Finasteride* is used in higher doses for the treatment of benign prostatic hyperplasia (see Chapter 43).] Adverse effects include decreased libido, decreased ejaculation, and erectile dysfunction. The drug should not be used or handled in pregnancy, as it can cause hypospadias in a male fetus. Use must be continued to maintain therapeutic benefits.

B. Minoxidil

Minoxidil [min-OX-i-dil], originally used as a systemic antihypertensive, was noted to have the adverse effect of increased hair growth. This adverse effect was turned into a therapeutic application in the treatment of alopecia. For hair loss, the drug is available as a nonprescription topical foam or solution. The topical formulation does not have antihypertensive effects. *Minoxidil* is effective at halting hair loss in both men and women and may produce hair growth in some patients. Although the mechanism of action is not fully known, it is believed to act, at least in part, by shortening the rest phase of the hair cycle. Like *finasteride*, the drug must be used continuously to maintain effects on hair growth. The main adverse effects include erythema and pruritus.

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Chapter Summary

- Acne vulgaris is a common disorder in individuals 12 to 24 years of age. Its pathogenesis is multifactorial with four main components: excessive androgen-induced sebum production, follicular proliferation of C. acnes, and an inflammatory response. Numerous agents can be used for acne,

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including include topical and oral antibiotics, *azelaic acid*, *benzoyl peroxide*, *dapsone*, retinoids, *salicylic acid*, and *sulfacetamide sodium*.

- For acne, combination therapy targeting the four pathogenic mechanisms is recommended, as it is often more effective than monotherapy, can reduce side effects, and may minimize resistance or tolerance to individual treatments. Therapy will generally need to continue for 8 weeks to assess full response and may need to continue for months or years.
- Several gram-positive and gram-negative bacteria can cause various superficial skin infections, such as folliculitis and impetigo, as well as deeper infections, such as erysipelas and cellulitis. Topical agents for superficial bacterial infections that target gram-positive bacteria are *bacitracin*, *mupirocin*, *ozenoxacin*, and *retapamulin.* Agents that target gram-negative bacteria are *gentamicin* and *polymyxin. Neomycin* is active against gram-negative and gram-positive organisms.
- Rosacea is a common inflammatory disorder affecting the central portion of facial skin including the cheeks, chin, forehead, and nose. Common agents used for rosacea include *brimonidine*, *doxycycline*, *ivermectin*, *metronidazole*, *minocycline*, and *oxymetazoline.*
- Pigmentation disorders include hypopigmentation conditions, such as vitiligo, and hyperpigmentation conditions. Agents for hyperpigmentation include *hydroquinone* and *tazarotene. Methoxsalen* is an oral photosensitizing agent used for treatment of hypopigmentation associated with vitiligo.
- Psoriasis is a chronic autoimmune skin disease that manifests as epidermal hyperplasia and dermal inflammation. It can cause significant social morbidity. Agents used for psoriasis include *apremilast*, biologics, *coal tar*, *salicylic acid*, *methotrexate*, retinoids, topical corticosteroids, and vitamin D analogs. *Methotrexate* is among the most commonly used systemic agents for psoriasis.
- Injectable biologics approved for moderate to severe psoriasis are antibody-based proteins produced by recombinant DNA technology. They target different cytokines important for psoriasis pathogenesis including TNF-α, IL-12/IL-23, and IL-17A.
- Alopecia (baldness) is the partial or complete loss of hair from areas where hair normally grows. Agents for alopecia include *finasteride* and *minoxidil.* Either drug must be used continuously to maintain effects on hair growth.

STUDY QUESTIONS

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Choose the ONE best answer.

45.1 Which of the following is correct regarding the use of isotretinoin in the treatment of acne?

A. It is used topically in the treatment of acne.
B. It acts primarily on the corticosteroid receptors.
C. It is used for milder forms of acne.
D. It is contraindicated in pregnancy.

Correct answer = D. Isotretinoin is an oral retinoid reserved for more severe forms of acne. Retinoic acids play an important role in mammalian embryogenesis. Excessive amounts of retinoids such as isotretinoin have been shown to cause teratogenicity, but the exact molecular mechanism is not known.

45.2 A 32-year-old woman with papulopustular rosacea prefers to use a topical agent, rather than an oral agent, to treat her lesions. Which of the following agents is the most appropriate recommendation?

A. Brimonidine
B. Doxycycline
C. Metronidazole
D. Oxymetazoline

Correct answer = C. Metronidazole is an antibacterial agent used topically for papulopustular rosacea. It is believed to work in rosacea through anti-inflammatory or immunosuppressive effects. Doxycycline is also used for papulopustular rosacea but is used orally rather than topically. Brimonidine and oxymetazoline are topical agents but are used for erythematotelangiectatic rosacea.

45.3 Which of the following drugs used for more severe forms of psoriasis works by reducing DNA synthesis in cells of the immune system and is noted for its long-term risk of liver damage?

A. Etanercept

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B. Calcipotriene
C. Tazarotene
D. Methotrexate

Correct answer = D. The primary mechanism of action of methotrexate is due to immunosuppressive activity, resulting from its ability to reduce DNA synthesis in cells of the immune system. The primary long-term risk is the potential for liver damage, and therefore, periodic liver function tests are required for patients using methotrexate.

45.4 Which of the following is correct regarding trichogenic agents?

A. Topically applied minoxidil is known for its hypotensive effects.
B. Once hair regrowth has been established with topically applied minoxidil, hair growth will be maintained after discontinuing its use.
C. Finasteride inhibits the 5α-reductase enzyme that controls the production of DHT from testosterone.
D. Both oral and topical minoxidil are commonly used for alopecia.

Correct answer = C. Androgenic alopecia is associated with DHT concentrations, and finasteride is known to inhibit the 5α-reductase enzyme required for the formation of DHT from testosterone. Only the topical form of minoxidil is used for the treatment of alopecia. Both minoxidil and finasteride must be continued to maintain effects on hair growth.

45.5 Which of the following topical anti-acne medications is the best recommendation if one of the goals is to reduce postinflammatory hyperpigmentation?

A. Azelaic acid
B. Minocycline
C. Benzoyl peroxide
D. Clindamycin

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Correct answer = A. Topical azelaic acid exhibits a lightening effect on hyperpigmented skin, which makes it useful in patients who experience dyspigmentation as a consequence of inflammatory acne.

45.6 A 16-year-old girl has mild acne on her face. Which of the following agents is the least appropriate choice for treating her acne?

A. Benzoyl peroxide
B. Topical clindamycin
C. Oral doxycycline
D. Adapalene

Correct answer = C. Oral antibiotics, such as doxycycline, are reserved for moderate to severe acne.

45.7 A 5-year-old boy presents with impetigo lesions around his lips. Which of the following topical agents is best to treat these lesions caused by S. aureus?

A. Gentamicin
B. Bacitracin
C. Mupirocin
D. Polymyxin

Correct answer = C. Mupirocin is a topical antibiotic that works by inhibiting protein synthesis targeting gram-positive organisms, such as S. aureus. It is useful in treating impetigo. Gentamicin and polymyxin target gram-negative bacteria. Bacitracin targets gram-positive bacteria but is used for prevention of infections.

45.8 A 45-year-old woman burned her hand while cooking dinner. Her skin blistered from the burn, and now the burned area is open. Which of the following topical medications is most appropriate to recommend to the patient for prevention of skin infection after a burn?

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A. Mupirocin
B. Bacitracin/polymyxin
C. Ozenoxacin
D. Retapamulin

Correct answer = B. This combination ointment containing both bacitracin and polymyxin is mostly used for the prevention of skin infections after burns or minor scrapes.

45.9 A 33-year-old man wants to quickly get his plaque psoriasis in visible areas under control for a planned trip to Jamaica and wants to keep it under control for at least the remainder of the summer. Which of the following therapeutic strategies for psoriasis would best enable the patient to achieve his goals?

A. Sequential therapy
B. Combination therapy
C. Monotherapy
D. Step-up therapy

Correct answer = A. Sequential therapy would likely be the best approach, as stronger and sometimes more toxic agents are used initially to rapidly clear the lesions, followed by less toxic agents for maintenance therapy.

45.10 A 32-year-old man presents to your clinic with rosacea characterized by erythema on his cheeks, chin, and forehead. Which of the following topical medications would be the best choice to treat the erythema?

A. Brimonidine
B. Ivermectin
C. Metronidazole
D. Minocycline

Correct answer = A. Brimonidine is an α_2 adrenoceptor agonist that reduces erythema through vasoconstriction.

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46

Clinical Toxicology

Dawn R. Sollee, Emily Jaynes Winograd

I. OVERVIEW

Toxicology is the study of poisons. For thousands of years, poisons have been woven into the rich fabric of the human experience. Homer and Aristotle described the poison arrow; Socrates was executed with poison hemlock; lead poisoning may have contributed to the fall of the Roman Empire; Marilyn Monroe, Elvis Presley, Prince, and Michael Jackson all fatally overdosed on prescription medications. Toxins can be inhaled, insufflated (snorted), orally ingested, injected, and absorbed dermally (Figure 46.1). An understanding of the varied mechanisms of toxicity helps to develop an approach to treatment. This chapter provides an overview of the emergent management of the poisoned patient, as well as a brief review of some of the more common and interesting toxins, their mechanisms, clinical presentations, and clinical management.

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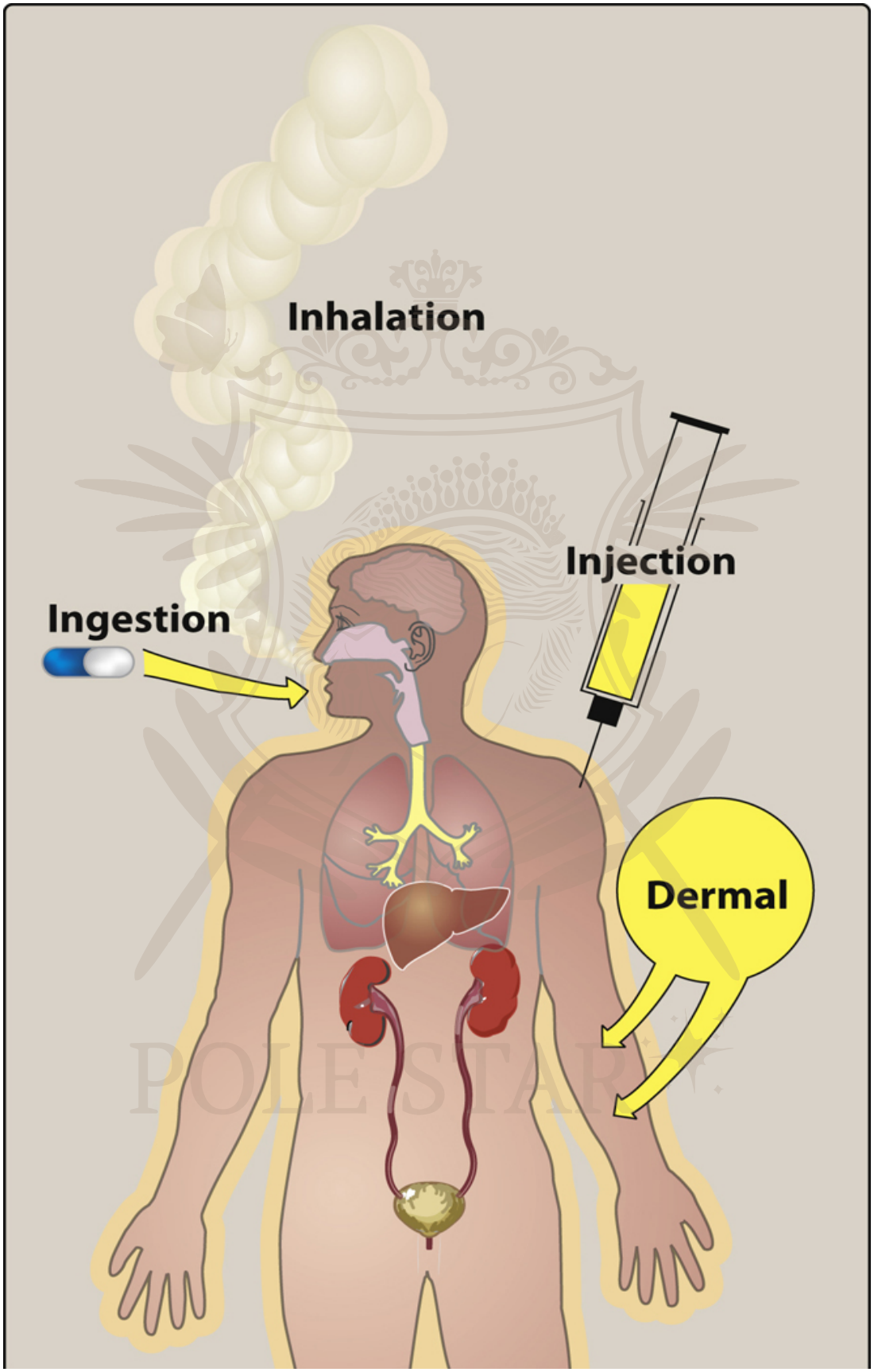

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Figure 46.1 Routes of exposure for toxins.

II. EMERGENCY TREATMENT OF THE POISONED PATIENT

The first principle in the management of the poisoned patient is to treat the patient, not the poison. Airway, breathing, and circulation are assessed and addressed initially, along with any other immediately life-threatening toxic effect (for example, profound increases or decreases in blood pressure, heart rate, respirations, or body temperature, or any dangerous cardiac dysrhythmias). Evaluating pH and electrolyte disturbances, plasma levels of drugs such as *acetaminophen* and salicylate, and assaying the blood for the appropriate drug screening analysis can further assist in instituting the best therapeutic regimen for the intoxicated patient. After administering oxygen, obtaining intravenous access, and placing the patient on hemodynamic monitors, the poisoned patient with an altered mental status should be given intravenous dextrose to treat potential hypoglycemia, a possible toxicological cause of altered mental status, *naloxone* to treat possible opioid or *clonidine* toxicity, and *thiamine* if ethanol-induced Wernicke encephalopathy is plausible.

Clinical Application 46.1 Naloxone Use in Opioid Overdose

Naloxone is an opioid receptor antagonist most commonly used to reverse life-threatening respiratory depression secondary to opioid overdose. *Naloxone* can be administered via multiple routes, though it is most often given intravenously or intranasally. Because of the relatively short duration of action of *naloxone* (~1 hour), repeat doses are sometimes necessary to maintain adequate symptom reversal. Patients requiring multiple repeated doses can be placed on a continuous *naloxone* infusion. While *naloxone* is a remarkably safe antidote, administering more than is required to reverse respiratory depression can precipitate opioid withdrawal symptoms including vomiting, diarrhea,

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tachycardia, hypertension, agitation, and combativeness. Interestingly, *naloxone* can also be considered for the reversal of bradycardia and hypotension caused by α_2-receptor agonists (for example, *clonidine*), though high doses may be required and efficacy can be limited.

A. Decontamination

Once the patient is stabilized, the need for decontamination can be assessed. This may include flushing the eyes with saline or tepid water to a neutral pH for ocular exposures, rinsing the skin for dermal exposures, and/or gastrointestinal (GI) decontamination with gastric lavage, activated charcoal, or whole bowel irrigation (utilizing a polyethylene glycol electrolyte balanced solution) for ingestions. GI decontamination therapy should be performed preferably within 1 hour of a toxic ingestion. Several substances do not adsorb to activated charcoal (for example, lead and other heavy metals, *iron*, *lithium*, *potassium*, and alcohols), limiting the use of activated charcoal in these instances unless there are coingested products.

B. Elimination enhancement

1.Hemodialysis: The elimination of some medications/toxins may be enhanced by hemodialysis if certain properties are met, such as low protein binding, small volume of distribution, small molecular weight, and water solubility of the toxin. Examples of medications or substances that can be removed with hemodialysis include methanol, ethylene glycol, salicylates, *theophylline*, *phenobarbital*, and *lithium*.

2.Urinary alkalinization: Alkalinization of the urine enhances the elimination of salicylates or *phenobarbital.* Increasing the urine pH with intravenous *sodium bicarbonate* transforms acidic drugs into an ionized form that prevents reabsorption, thereby trapping it in the urine to be excreted by

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the kidney. The goal urine pH is 7.5 to 8, while ensuring the serum pH does not exceed 7.55.

3.Multiple-dose activated charcoal: Multiple-dose activated charcoal enhances the elimination of certain drugs (for example, *theophylline*, *phenobarbital*, *digoxin*, *carbamazepine*, *quinine*). Activated charcoal is extremely porous and has a high surface area, which creates a gradient across the lumen of the gut. Medications traverse from areas of high concentration to low concentration, promoting absorbed medication to cross back into the gut to be adsorbed by the activated charcoal. In addition, activated charcoal blocks the reabsorption of medications that undergo enterohepatic recirculation (for example, *phenytoin*), by adsorbing the substance to the activated charcoal (Figure 46.2). Bowel sounds must be present prior to each activated charcoal dose to prevent obstruction.

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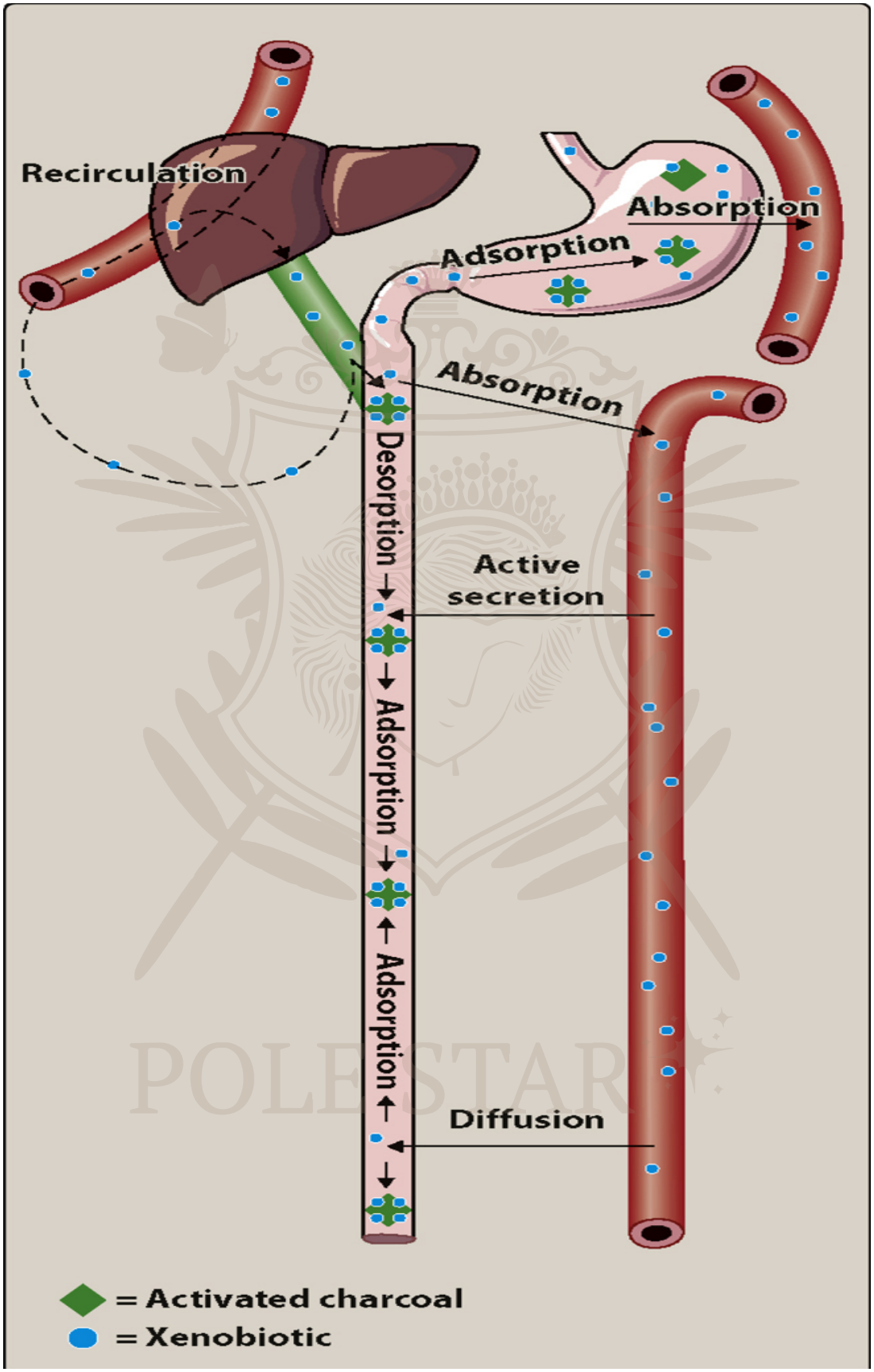
Recirculation
Absorption
Adsorption
Absorption
Desorption
Active secretion
Adsorption
Adsorption
Diffusion
= Activated charcoal
= Xenobiotic

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Figure 46.2 Mechanism of multiple-dose activated charcoal.

III. SELECT PHARMACEUTICAL AND OCCUPATIONAL TOXICITIES

A. Acetaminophen

Acetaminophen produces toxicity when normal metabolic pathways become saturated, leading to the production of a hepatotoxic metabolite (*N*-acetyl-*p*-benzoquinone imine, NAPQI) (Figure 46.3). After therapeutic doses of *acetaminophen*, the liver generates glutathione, which detoxifies NAPQI. However, in overdose, glutathione is depleted, leaving the metabolite to produce toxicity. There are four phases typically describing *acetaminophen* toxicity (Figure 46.4). The antidote for *acetaminophen* toxicity, *N-acetylcysteine* (*NAC*), works as a glutathione precursor and glutathione substitute and assists with sulfation. *NAC* may also function as an antioxidant to aid in recovery. *NAC* is most effective when initiated within 8 to 10 hours of ingestion. The Rumack–Matthew nomogram (Figure 46.5), which is based on the time of ingestion and the serum *acetaminophen* level, is utilized after an acute ingestion to determine if *NAC* therapy is needed. The nomogram is helpful to predict *acetaminophen* toxicity when levels can be obtained between 4 and 24 hours post ingestion. If untreated, *acetaminophen* toxicity leads to acute liver failure, cerebral edema, coma, and death.

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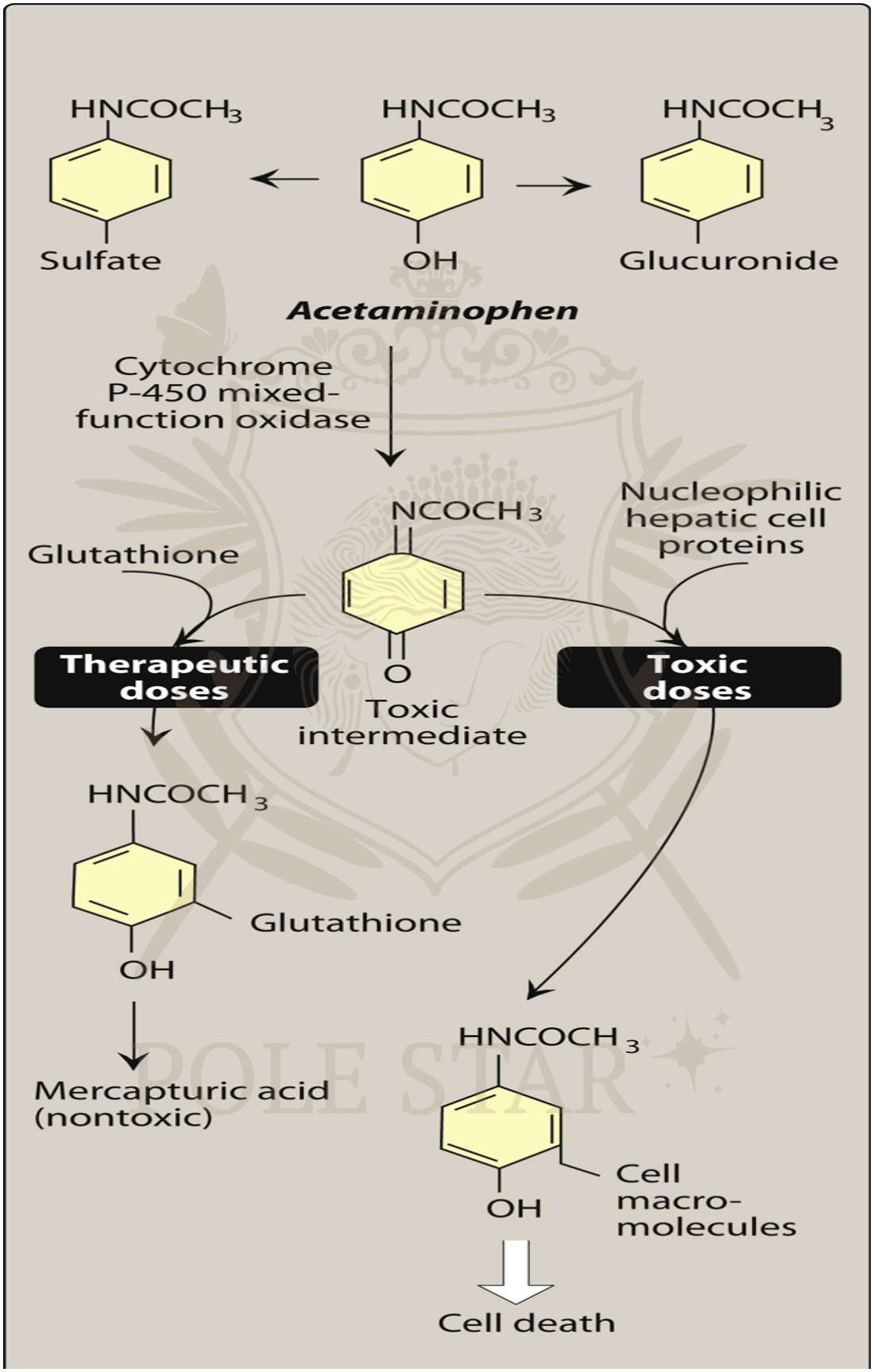
HNCOCH3
HNCOCH3
HNCOCH3
Sulfate
OH
Glucuronide
Acetaminophen
Cytochrome P-450 mixed-function oxidase
NCOCH3
Nucleophilic hepatic cell proteins
Glutathione
Therapeutic doses
Toxic doses
O
Toxic intermediate
HNCOCH3
Glutathione
OH
Mercapturic acid (nontoxic)
HNCOCH3
Cell macro-molecules
OH
Cell death

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Figure 46.3 Metabolism of *acetaminophen*.

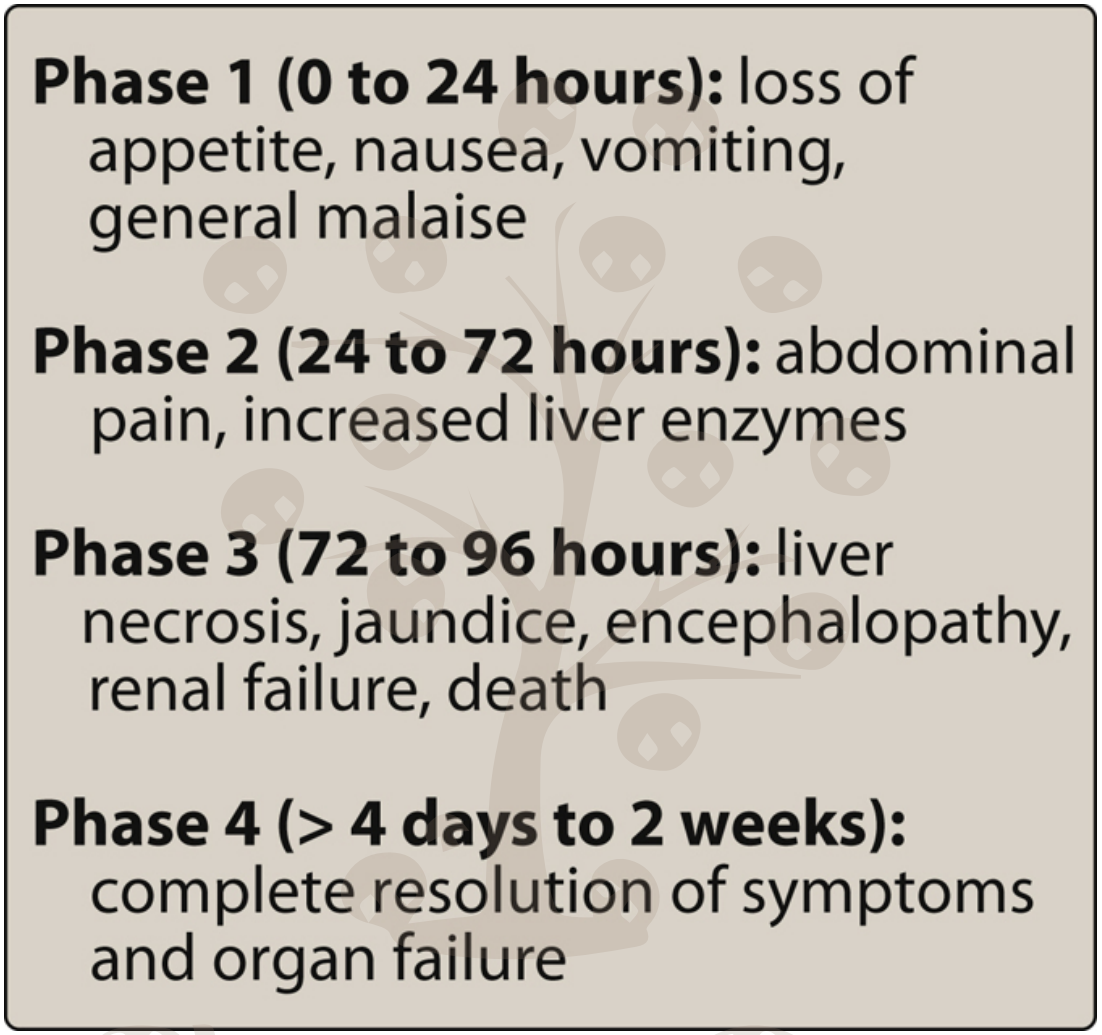

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Figure 46.4 Phases of *acetaminophen* toxicity.

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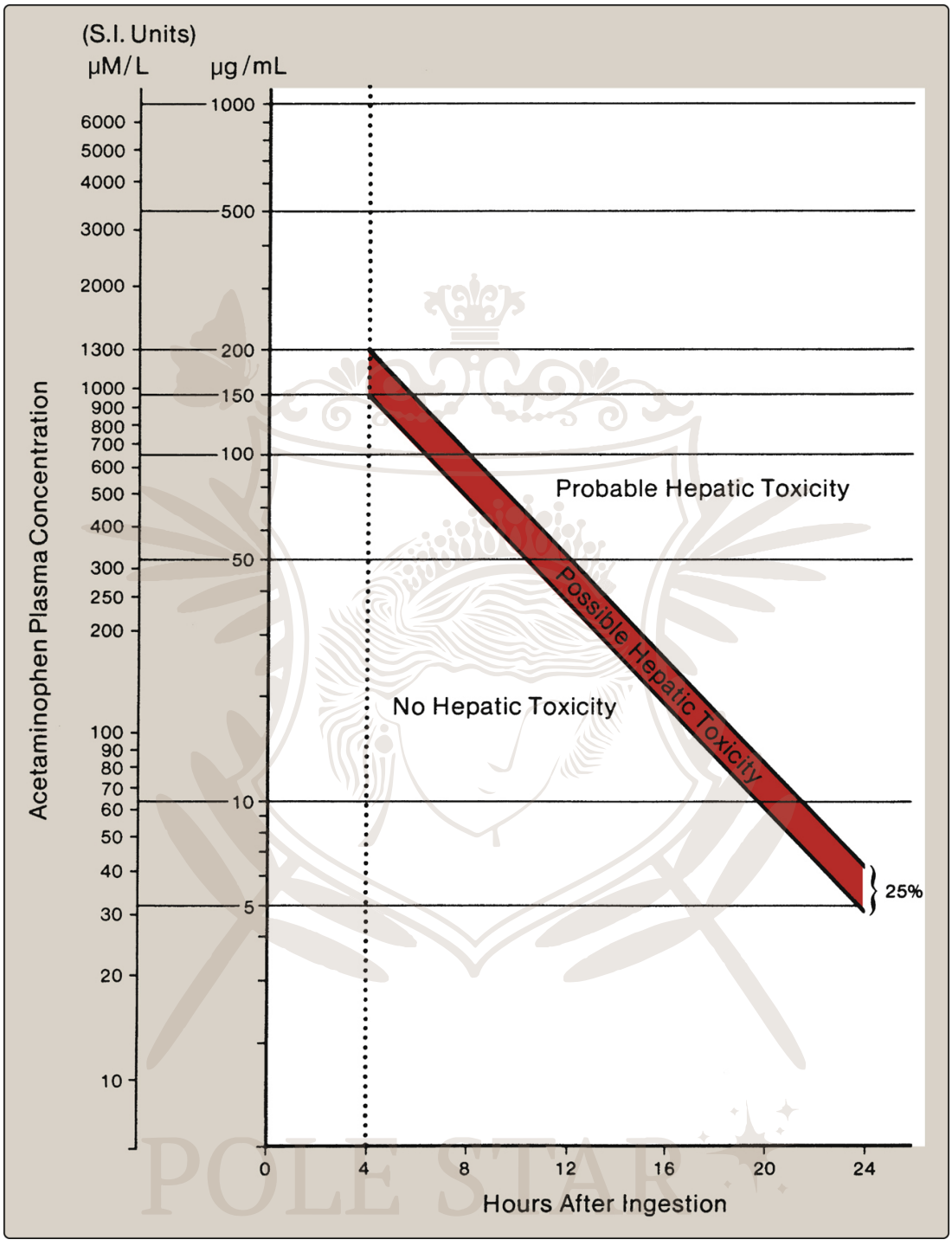

Figure 46.5 Rumack-Matthew nomogram for *acetaminophen* poisoning.*Acetaminophen* concentration plotted versus time after exposure to predict potential toxicity and antidote use.Reprinted from B. H.Rumack . *Acetaminophen* overdose in children and adolescents. *Pediatr. Clin. North Am*. 33: 691 (1986), with permission from Elsevier.

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B. Alcohols

1.Methanol (wood alcohol) and ethylene glycol: Methanol is found in products like windshield washer fluid and model airplane fuel. Ethylene glycol is most commonly found in radiator antifreeze. These primary alcohols are relatively nontoxic and mainly cause central nervous system (CNS) depression. However, methanol and ethylene glycol are oxidized to toxic products: formic acid in the case of methanol, and glycolic, glyoxylic, and oxalic acids in the case of ethylene glycol. *Fomepizole* [foe-MEP-i-zole] inhibits this oxidative pathway by blocking alcohol dehydrogenase. [Note: Ethanol is an alternative alcohol dehydrogenase inhibitor if *fomepizole* is not available.] It prevents the formation of toxic metabolites and allows the parent alcohols to be excreted by the kidney (Figure 46.6). Hemodialysis is often utilized to remove the toxic acids that are already produced. In addition, cofactors are administered to encourage metabolism to nontoxic metabolites (*folate* for methanol, *thiamine* and *pyridoxine* for ethylene glycol). If untreated, methanol ingestion may produce blindness, metabolic acidosis, seizures, and coma. Ethylene glycol ingestion may lead to renal failure, hypocalcemia, metabolic acidosis, and heart failure.

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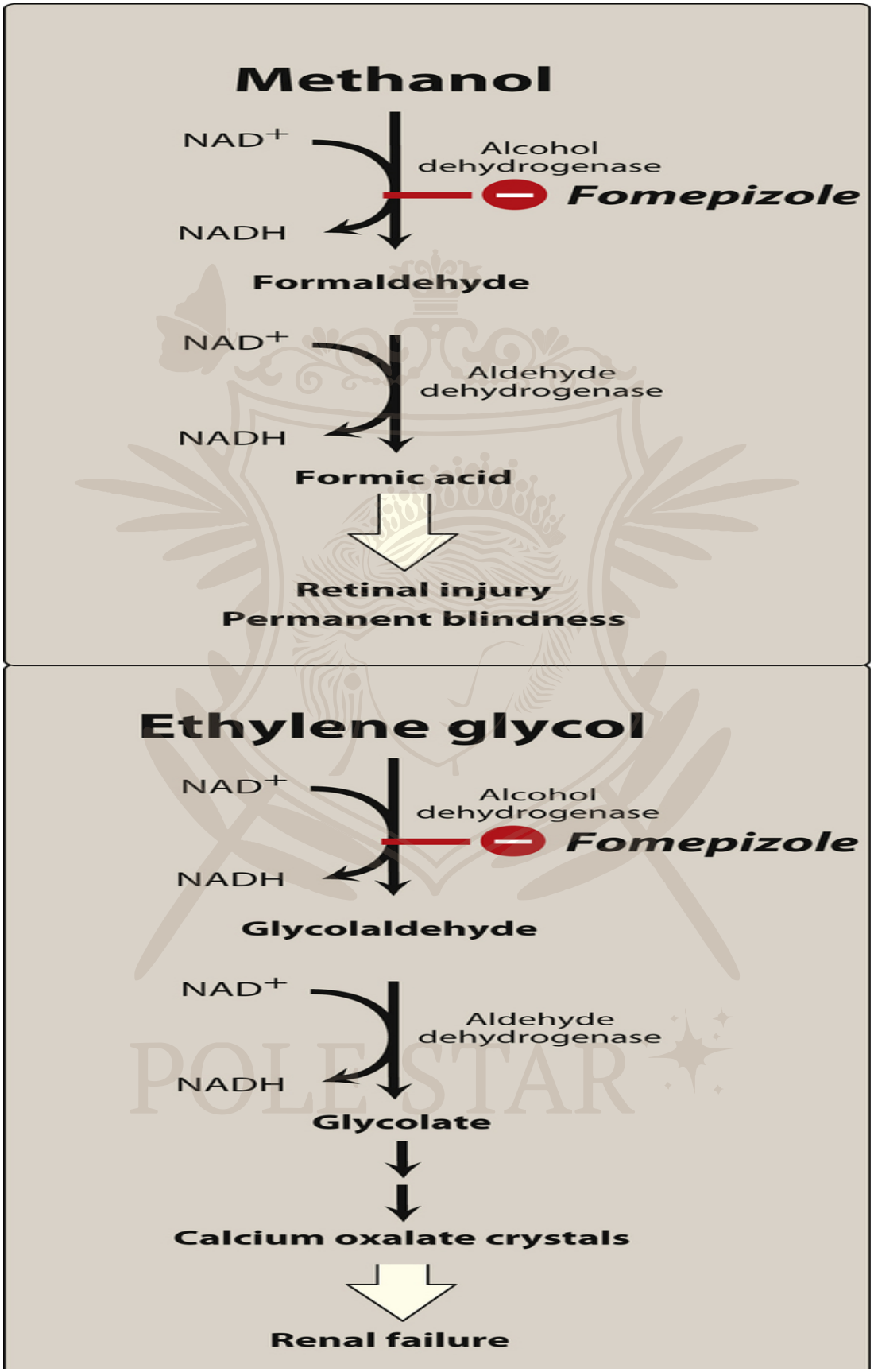
Methanol
NAD+
NADH
Alcohol dehydrogenase
Fomepizole
Formaldehyde
NAD+
NADH
Aldehyde dehydrogenase
Formic acid
Retinal injury
Permanent blindness
Ethylene glycol
NAD+
NADH
Alcohol dehydrogenase
Fomepizole
Glycolaldehyde
NAD+
NADH
Aldehyde dehydrogenase
Glycolate
Calcium oxalate crystals
Renal failure

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Figure 46.6 Metabolism of methanol and ethylene glycol.

2.Isopropanol (rubbing alcohol, isopropyl alcohol): This secondary alcohol is metabolized to acetone via alcohol dehydrogenase. Acetone cannot be further oxidized to carboxylic acids, and therefore, acidemia does not occur. Because isopropyl alcohol is not metabolized to a toxic metabolite, no antidote is necessary to treat an isopropyl alcohol ingestion. Isopropanol is a known CNS depressant (approximately twice as intoxicating as ethanol) and GI irritant. Therefore, treatment centers on supportive care.

C. Carbon monoxide

Carbon monoxide is a colorless, odorless, and tasteless gas. It is a natural by-product of the combustion of carbonaceous materials, and common sources of this gas include automobiles, poorly vented furnaces, fireplaces, wood-burning stoves, kerosene space heaters, house fires, charcoal grills, and generators. Following inhalation, carbon monoxide rapidly binds to hemoglobin to produce carboxyhemoglobin. The binding affinity of carbon monoxide to hemoglobin is 230 to 270 times greater than that of oxygen. Consequently, even low concentrations of carbon monoxide in the air can produce significant levels of carboxyhemoglobin. In addition, bound carbon monoxide increases hemoglobin affinity for oxygen at the other oxygen-binding sites. This high-affinity binding of oxygen prevents the unloading of oxygen at the tissues, further reducing oxygen delivery (Figure 46.7). The presence of this highly oxygenated blood may produce "*cherry red*" lips and mucous membranes. Carbon monoxide toxicity can also occur following inhalation or ingestion of methylene chloride found in paint strippers. Once absorbed, methylene chloride is metabolized to carbon monoxide through the hepatic cytochrome P450 pathway. The symptoms of carbon monoxide intoxication are consistent with hypoxia,

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including headache, dyspnea, lethargy, confusion, and drowsiness. Higher exposure levels can lead to seizures, coma, and death. Long-term neurocognitive effects such as dementia and personality changes are unpredictable and can be delayed in onset. The management of a carbon monoxide–poisoned patient includes prompt removal from the source of carbon monoxide and institution of 100% oxygen by nonrebreathing face mask, high flow nasal cannula, or endotracheal tube. In patients with severe intoxication, oxygenation in a hyperbaric chamber may be warranted.

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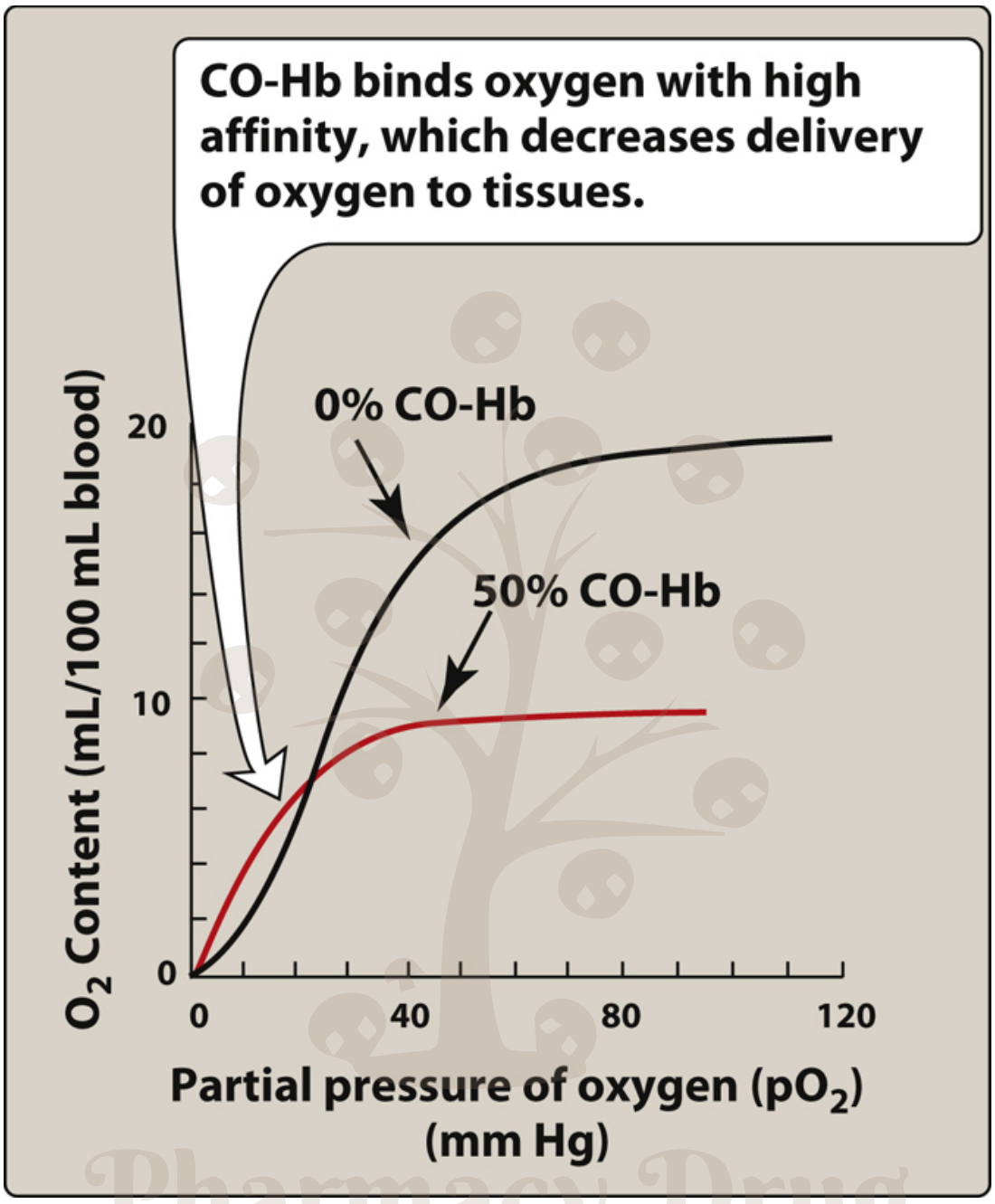

Figure 46.7 Effect of carbon monoxide on the oxygen affinity of hemoglobin.CO-Hb = carboxyhemoglobin.

D. Cyanide

Cyanide is one of the toxic products of combustion produced during house fires. Its principal toxicity occurs as a result of the

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inactivation of the enzyme cytochrome oxidase (cytochrome a_3), leading to the inhibition of cellular respiration. Therefore, even in the presence of oxygen, tissues with a high oxygen demand such as the brain and heart are adversely affected. Death can occur quickly due to arrest of oxidative phosphorylation and production of adenosine triphosphate (ATP). The antidote, *hydroxocobalamin* (vitamin B_{12a}), is administered intravenously to bind the cyanide and produce *cyanocobalamin* (vitamin B_{12}) without the adverse effects of hypotension or methemoglobin production seen with previous antidotes. The previous cyanide antidote kit consisted of *sodium nitrite* to form cyanomethemoglobin and *sodium thiosulfate* to accelerate the production of thiocyanate, which is much less toxic than cyanide and is quickly excreted in urine. To prevent the oxygen-carrying capacity becoming too low in patients with smoke inhalation and cyanide toxicity, the induction of methemoglobin with *sodium nitrite* should be avoided unless the carboxyhemoglobin concentration is less than 10%.

E. Iron

The incidence of pediatric iron toxicity has greatly diminished during the past 2 decades due to education and changes in packaging and labeling of iron products. Iron is radiopaque and may be visible on an abdominal radiograph if the product contains a sufficient concentration of elemental iron. Toxic effects can be expected with ingestions as little as 20 mg/kg of elemental iron, and doses of 60 mg/kg may be lethal. Each iron salt contains a different concentration of elemental iron (Figure 46.8). A serum iron level should be obtained, since levels between 500 and 1000 µg/dL have been associated with shock and levels higher than 1000 µg/dL with death. Patients with iron toxicity usually present with nausea, vomiting, and abdominal pain. Depending on the amount of elemental iron ingested, the patient may experience a latent period or may progress quickly to hypovolemia, metabolic acidosis, hypotension, and coagulopathy. Ultimately, hepatic failure and multisystem failure, coma, and death may occur.

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Deferoxamine [de-fer-OKS-a-meen], an iron-specific chelator, binds free iron, creating ferrioxamine, which is excreted in the urine. Hypotension may occur if rapid intravenous boluses of *deferoxamine* are administered instead of a continuous infusion.

Content	Elemental iron (%)
Ferrous fumarate	33
Ferrous gluconate	12
Ferrous sulfate	20

Figure 46.8 Elemental iron contained in various iron preparations.

F. Lead

Lead is ubiquitous in the environment, with sources of exposure including old paint, drinking water, industrial pollution, food, and contaminated dust. Most chronic exposure to lead occurs with inorganic lead salts, such as those in paint used in housing constructed prior to 1978. Adults absorb approximately 10% of ingested lead, whereas children absorb about 40%. Inorganic forms of lead are initially distributed to the soft tissues and more slowly redistribute to bone, teeth, and hair. Lead impairs bone formation and causes increased calcium deposition in long bones visible on X-ray. Ingested lead is radiopaque and may appear on an abdominal radiograph if present in the GI tract. Lead has an apparent blood half-life of about 1 to 2 months, whereas its half-life in the bone is 20 to 30 years. Chronic exposure to lead can

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have serious effects on several tissues (Figure 46.9). Early symptoms of lead toxicity can include discomfort and constipation (and, occasionally, diarrhea), whereas higher exposures can produce painful intestinal spasms. CNS effects from lead include headaches, confusion, clumsiness, insomnia, fatigue, and impaired concentration. As the disease progresses, clonic convulsions and coma can occur. Death is rare, given the ability to treat lead intoxication with chelation therapy. Blood levels of 5 to 20 µg/dL in children have been shown to lower IQ in the absence of other symptoms. Finally, lead can cause hypochromic, microcytic anemia as a result of a shortened erythrocyte life span and disruption of heme synthesis.

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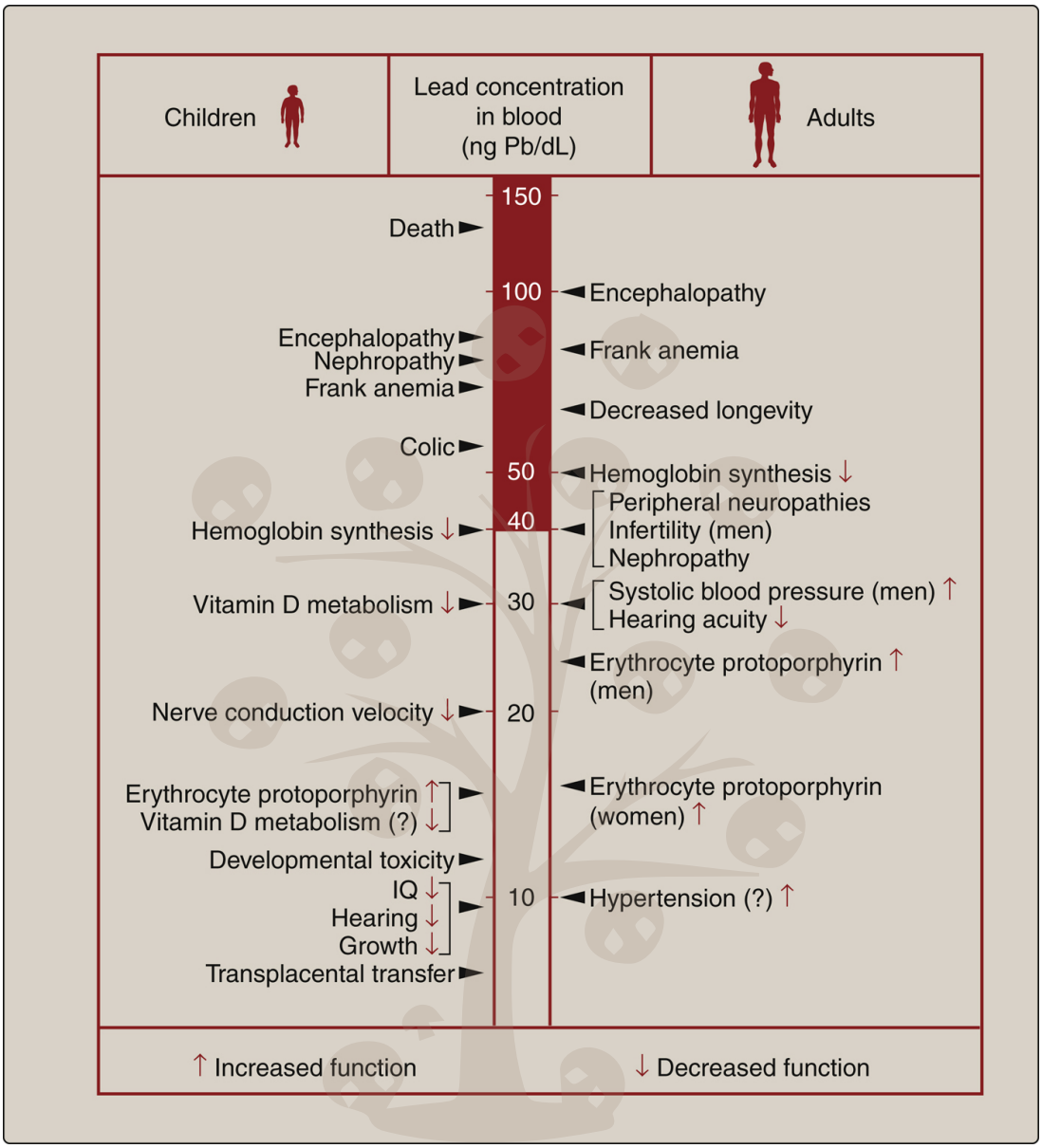

Figure 46.9 Comparison of effects of lead on children and adults.From the Centers for Disease Control and Prevention. http://wonder.cdc.gov/

Multiple chelators are available for the treatment of lead toxicity. When levels are greater than 45 µg/dL, but less than 70 µg/dL in children, *succimer* (*dimercaptosuccinic acid* [*DMSA*]), an oral chelator, is the treatment of choice. With lead levels greater than 70 µg/dL or if encephalopathy is present, dual parenteral therapy is required with *dimercaprol* given intramuscularly and *calcium*

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disodium edetate given intravenously. *Dimercaprol* is suspended in peanut oil and should not be administered to those with a peanut allergy.

G. Organophosphate and carbamate insecticides

These insecticides exert their toxicity through inhibition of acetylcholinesterase, with subsequent accumulation of excess acetylcholine producing nicotinic (mydriasis, fasciculations, muscle weakness, tachycardia, hypertension) and muscarinic (diarrhea, urination, miosis, bradycardia, bronchorrhea, bronchospasm, emesis, lacrimation, salivation) effects. Carbamates reversibly bind to acetylcholinesterase, whereas organophosphates undergo an aging process to ultimately irreversibly inactivate the enzyme. Organophosphate nerve agents, such as sarin, soman, tabun, and most recently Novichok, have the same mechanism of action, but the aging process is much more rapid compared to insecticides. *Atropine*, a muscarinic receptor antagonist, and *pralidoxime*, an oxime to reactivate cholinesterase, should be administered intravenously or intramuscularly to treat the muscarinic and nicotinic effects, respectively (see Chapter 4).

IV. ANTIDOTES

Specific chemical antidotes for poisoning have been developed for a number of chemicals or classes of toxicants (Figure 46.10). This is not an all-inclusive list.

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POISON	ANTIDOTE(S)
Acetaminophen	*N-Acetylcysteine*
Anticholinergic agents (antihistamines, etc.)	*Physostigmine*
Arsenic	*Dimercaprol, succimer (dimercaptosuccinic acid, DMSA), dimercaprol*
Benzodiazepine	*Flumazenil*
Carbon monoxide	Oxygen (± hyperbaric chamber)
Cyanide	*Hydroxocobalamin, sodium nitrite,* and *sodium thiosulfate*
Dabigatran	*Idarucizumab*
Digitalis	*Digoxin-immune Fab*
Heparin	*Protamine sulfate*
Hydrofluoric acid	*Calcium*
Iron	*Deferoxamine*
Isoniazid and Gyromitra mushrooms	*Pyridoxine*
Lead	*Calcium disodium edetate, dimercaprol, succimer (dimer-captosuccinic acid, DMSA)*
Methanol and ethylene glycol	*Fomepizole*
Methemoglobinemia	*Methylene blue*
Opiates, *clonidine*	*Naloxone*
Organophosphates, nerve gases	*Atropine, pralidoxime*
Rivaroxaban or *apixaban*	*Factor Xa*
Warfarin	*Vitamin K1 (phytonadione)*

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Figure 46.10 Common antidotes.

Chapter Summary

- Treatment of the poisoned patient should be tailored to the individual clinical presentation and symptoms, not the suspected toxicant.
- Once the poisoned patient has been stabilized, decontamination (for example, flushing the eyes/skin for topical exposures, administering activated charcoal for certain oral exposures) and enhanced elimination of amenable substances should be considered.
- *Acetaminophen* overdose is characterized by GI symptoms and hepatotoxicity due to the formation of NAPQI. *N*-a*cetylcysteine* is the antidote.
- While both methanol and ethylene glycol ingestion cause metabolic acidosis, methanol may also cause visual disturbances and blindness, while ethylene glycol is more likely to cause renal failure, hypocalcemia, and heart failure. Hallmarks of isopropanol (isopropyl alcohol) ingestion include significant GI irritation and CNS depression without metabolic acidosis.
- Symptoms of carbon monoxide exposure are secondary to hypoxia and range from headache and lethargy to seizure, coma, and death. Treatment includes removing the patient from the source of exposure and administering 100% oxygen, and in severe cases hyperbaric oxygen.
- Cyanide is a mitochondrial poison that inhibits cellular respiration via inactivation of cytochrome oxidase. The antidote, *hydroxocobalamin*, binds cyanide to form nontoxic cyanocobalamin (vitamin B_{12}).
- Iron toxicity initially manifests as GI symptoms that progress to hypovolemia, metabolic acidosis, hypotension, and multisystem organ failure. *Deferoxamine* can be used to chelate iron in severe toxicity.
- Clinical effects of lead poisoning vary depending on patient age and degree of exposure. Chelators can be used to treat significantly elevated blood lead levels or encephalopathy.
- Organophosphate insecticides inhibit acetylcholinesterase, leading to muscarinic cholinergic symptoms including diarrhea, urination, miosis, bradycardia, bronchorrhea/bronchospasm, emesis, lacrimation, and salivation (DUMBBELS).
- The majority of poisons do not have a specific antidote. Supportive care is the mainstay of treatment for most poisonings.

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STUDY QUESTIONS

Choose the ONE best answer.

46.1A 3-year-old boy is brought to the emergency department by his mother, who reports that he has been crying continuously and "*does not want to play or eat*" for the past few days. She also states that he has not had regular bowel movements, with mostly constipation and occasional diarrhea, and frequently complains of abdominal pain. The child now has an altered level of consciousness, is difficult to arouse, and begins to have tonic-clonic movements. The clinician rules out infection and other medical causes. Upon questioning, the mother states that the house is in an older neighborhood, that her house has not been remodeled or repainted since the 1940s, and that the paint is chipping around the windows and doors. The child is otherwise breathing on his own and urinating normally. Which of the following toxins would you expect to be producing such severe effects in this child?

A. Iron
B. Lead
C. Carbon monoxide
D. Cyanide

Correct answer = B. Lead poisoning is common among children in older homes painted before lead was removed from paint. Paint chips and dust with lead are easily ingested by toddlers, and excessively high lead levels can lead to the signs and symptoms described plus clumsiness, confusion, headaches, coma, constipation, intestinal spasms, and anemia. Death is rare when chelation therapy is instituted. Iron can produce abdominal pain, but more often would cause diarrhea, vomiting, and volume loss. Carbon monoxide would affect the entire household, depending on the source. Clinical effects from carbon monoxide would include headache, nausea, and CNS depression. If he had cyanide poisoning, death would have occurred quickly following respiratory arrest of oxidative phosphorylation and production of adenosine triphosphate, but this child has been exhibiting symptoms over several days.

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46.2 A family consisting of a 31-year-old woman, 3-year-old girl, and 8-month-old girl presents to the emergency department. The children are vomiting and listless, and the mother complains of nausea, vomiting, and dizziness. The mother reports that their electricity has been out, and they have been using a generator to power the air conditioning. Arterial blood gas reveals elevated carboxyhemoglobin levels suggestive of carbon monoxide toxicity in all three patients. What antidote should be administered for carbon monoxide poisoning for this family?

A. 100% oxygen administered via a non-rebreather mask
B. Methylene blue
C. Hydroxocobalamin
D. Fomepizole

Correct answer = A. With the administration of 100% oxygen, the half-life of the carbon monoxide is decreased from 4 to 6 hours to approximately 60 minutes, thereby increasing the elimination of the carbon monoxide. Methylene blue is the antidote for methemoglobinemia. Hydroxocobalamin is the antidote for cyanide toxicity. Fomepizole is the antidote for methanol or ethylene glycol toxicity.

46.3 A 50-year-old migrant field worker comes to the emergency department and complains of diarrhea, tearing, nausea and vomiting, and sweating. The clinician notices that he looks generally anxious and has fine fasciculations in the muscles of the upper chest as well as pinpoint pupils. Which of the following antidotes should he receive first?

A. *N*-acetylcysteine
B. Sodium nitrite
C. Deferoxamine
D. Atropine

Correct answer = D. Atropine is appropriate for this patient, who has symptoms consistent with organophosphate (insecticide) poisoning. The mnemonic

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DUMBBELS (diarrhea, urination, miosis, bronchorrhea/bronchospasm, bradycardia, emesis, lacrimation, salivation) can be used to remember the signs and symptoms of cholinergic toxicity. An anticholinergic antidote, atropine, controls these muscarinic symptoms, whereas the antidote pralidoxime treats the nicotinic symptoms like fasciculations (involuntary muscle quivering or twitching). *N*-acetylcysteine is the antidote for acetaminophen overdose and acts as a sulfhydryl donor. Sodium nitrite is one of the antidotes included in the old cyanide antidote kit (sodium nitrite and sodium thiosulfate). Deferoxamine is the chelating agent for iron.

46.4 A 45-year-old man presented to the emergency department 18 hours after ingesting an unknown product. On presentation, he is tachycardic, hypertensive, tachypneic, and complaining of flank pain. A metabolic panel is obtained, and the patient has a large anion gap acidosis, an increased creatinine, and hypocalcemia. Which of the following substances was most likely ingested?

A. Methanol
B. Acetaminophen
C. Ethylene glycol
D. Iron

Correct answer = C. Ethylene glycol produces a metabolic acidosis from the toxic metabolites. The formation of calcium oxalate crystals, which can be found on urinalysis, leads to hypocalcemia and renal failure. The treatment regimen for this patient would include intravenous fomepizole, if some of the parent compound was still present, and hemodialysis. Methanol may produce a metabolic acidosis as well, but its target organ of toxicity is the eyes instead of the kidneys as with ethylene glycol. Acetaminophen toxicity may produce upper quadrant pain within the first 24 hours, but vital sign abnormalities are not usually found during this time frame. Iron toxicity may also produce a metabolic acidosis and tachycardia. However, hypocalcemia does not occur.

46.5 A 33-year-old, 82-kg woman presents to the emergency department 3 hours after ingesting "*a whole bottle*" of acetaminophen tablets. The patient complains of nausea, vomiting, and abdominal pain. An acetaminophen level 4 hours

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after ingestion is 227 µg/mL. Based on the Rumack–Matthew nomogram, what is the likelihood that this patient will experience hepatotoxicity secondary to her ingestion?

A. No hepatic toxicity expected
B. Possible hepatic toxicity
C. Probable hepatic toxicity
D. The level is uninterpretable because it was drawn too soon following ingestion and cannot be plotted on the nomogram.

Correct answer = C. Levels greater than 200 *µ*g/mL 4 hours following an acute ingestion indicate probable hepatic toxicity. Administration of *N*-acetylcysteine is warranted. Levels drawn earlier than 4 hours post-ingestion cannot be plotted on the Rumack–Matthew nomogram. However, because this level was drawn 4 hours after an acute ingestion, it is appropriate to use the nomogram to assess potential toxicity and antidote use.

46.6 A 15-year-old girl presents to the emergency department with CNS depression. She is bradycardic and hypotensive. Upon further questioning, the mother admits that the patient was found with an open bottle of clonidine. Which antidote might be beneficial for this patient?

A. Flumazenil
B. Atropine
C. Deferoxamine
D. Naloxone

Correct answer = D. Naloxone has a reversal rate of the CNS effects of approximately 50% in clonidine ingestions. Flumazenil reverses benzodiazepines and has no effect on clonidine. Atropine is an anticholinergic agent and would not improve the CNS depression. Deferoxamine is the chelator for iron.

46.7 A 45-year-old woman presents to the emergency department with a complaint of persistent vomiting. The patient

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appears intoxicated, but an ethanol level returns as negative and her basic metabolic panel is unremarkable. Which of the following substances did she probably ingest?

A. Isopropyl alcohol
B. Methanol
C. Ethylene glycol
D. Ethanol

Correct answer = A. Isopropyl alcohol produces twice as much CNS depression as ethanol and is known to cause GI distress. Isopropyl alcohol is metabolized to acetone, so a metabolic acidosis does not result (which is in contrast to the acidosis generated by methanol and ethylene glycol). The ethanol level was negative, eliminating ethanol as an ingestion.

46.8 A 4-year-old, 16-kg boy presents to the emergency department after ingesting 10 of his mother's prenatal vitamins. Each tablet contains ferrous fumarate 81 mg. How many mg/kg of elemental iron did the patient reportedly ingest?

A. 5 mg/kg
B. 16.9 mg/kg
C. 50.6 mg/kg
D. 0.6 mg/kg

Correct answer = B. Ferrous fumarate is 33% elemental iron; therefore, each 81 mg tablet of ferrous fumarate contains 27 mg of elemental iron (81 mg × 33% = 27 mg). The patient reportedly ingested 10 tablets, for a total ingestion of 270 mg of elemental iron (27 mg × 10 tablets = 270 mg). He weighs 16 kg; 270 mg of elemental iron ÷ 16 kg = 16.9 mg/kg. Significant toxicity is not anticipated following ingestion of this quantity of iron.

46.9 Emergency personnel are called to evaluate a 75-year-old man who was found unconscious in his home. On arrival, the paramedics find the patient unresponsive with several unidentified pills strewn on the floor around him. What is the first step in managing this patient?

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A. Induce vomiting to clear the stomach of any pills the patient may have ingested
B. Administer oxygen and establish IV access
C. Give naloxone 0.4 mg IV
D. Assess airway, breathing, and circulation

Correct answer = D. Assessing and addressing airway, breathing, and circulation is the first step in managing any medical emergency, including poisoning and drug overdose. In practice, if there are multiple rescuers available, this initial assessment often occurs in conjunction with administering oxygen and establishing IV access. Naloxone, given either intranasally or intravenously, should be considered in this patient once the primary assessment of airway, breathing, and circulation has been completed. Induction of emesis is not a recommended modality for GI decontamination due to aspiration risk and limited efficacy.

46.10 A 47-year-old man with a history of a seizure disorder, maintained on phenytoin, presented to the emergency department with salicylate toxicity. The salicylate level was 50 mg/dL (15-35 mg/dL therapeutic range) and the phenytoin level was 15 mg/L (10-20 mg/L therapeutic range). What therapy can be considered to enhance the elimination of salicylate without impacting the phenytoin?

A. Multiple doses of activated charcoal
B. Urinary alkalinization
C. Whole bowel irrigation
D. Urinary acidification

Correct answer = B. Urinary alkalinization enhances the elimination of the salicylate but does not affect the therapeutic phenytoin level. Multiple doses of activated charcoal would lower the concentration of both medications, rendering the phenytoin subtherapeutic. Whole bowel irrigation is another GI decontamination modality involving administration of large quantities (up to 2 L/h in adults) of a polyethylene glycol–balanced electrolyte solution via a nasogastric tube until the patient generates clear rectal effluent.

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47

Drugs of Abuse

Carol Motycka, Joseph Spillane

I. OVERVIEW

Excessive use or misuse of drugs for intoxicating or mind-altering effects is considered substance misuse, and those who misuse substances are considered to have a substance use disorder. In order to understand substance use disorders, it is important to recognize the difference between physical dependence and addiction. Physical dependence may occur after chronic use of a drug, whether it was used as instructed or not. Two attributes of physical dependence include tolerance and withdrawal. Tolerance is the need to use more of a drug in order to have the same desired effect, while withdrawal occurs after abrupt cessation of a drug. Withdrawal may consist of both mental and physical symptoms, some of which may be life threatening (for example, convulsions). Addiction is recognized as the compulsive use of a drug with the inability to stop using the substance, despite suffering negative consequences such as loss of employment or failure to meet family obligations. Addiction is a psychological dependence. Individuals with addiction often present with concomitant physical dependence, secondary to chronic use of the drug. Figure 47.1 provides a list of commonly abused substances.

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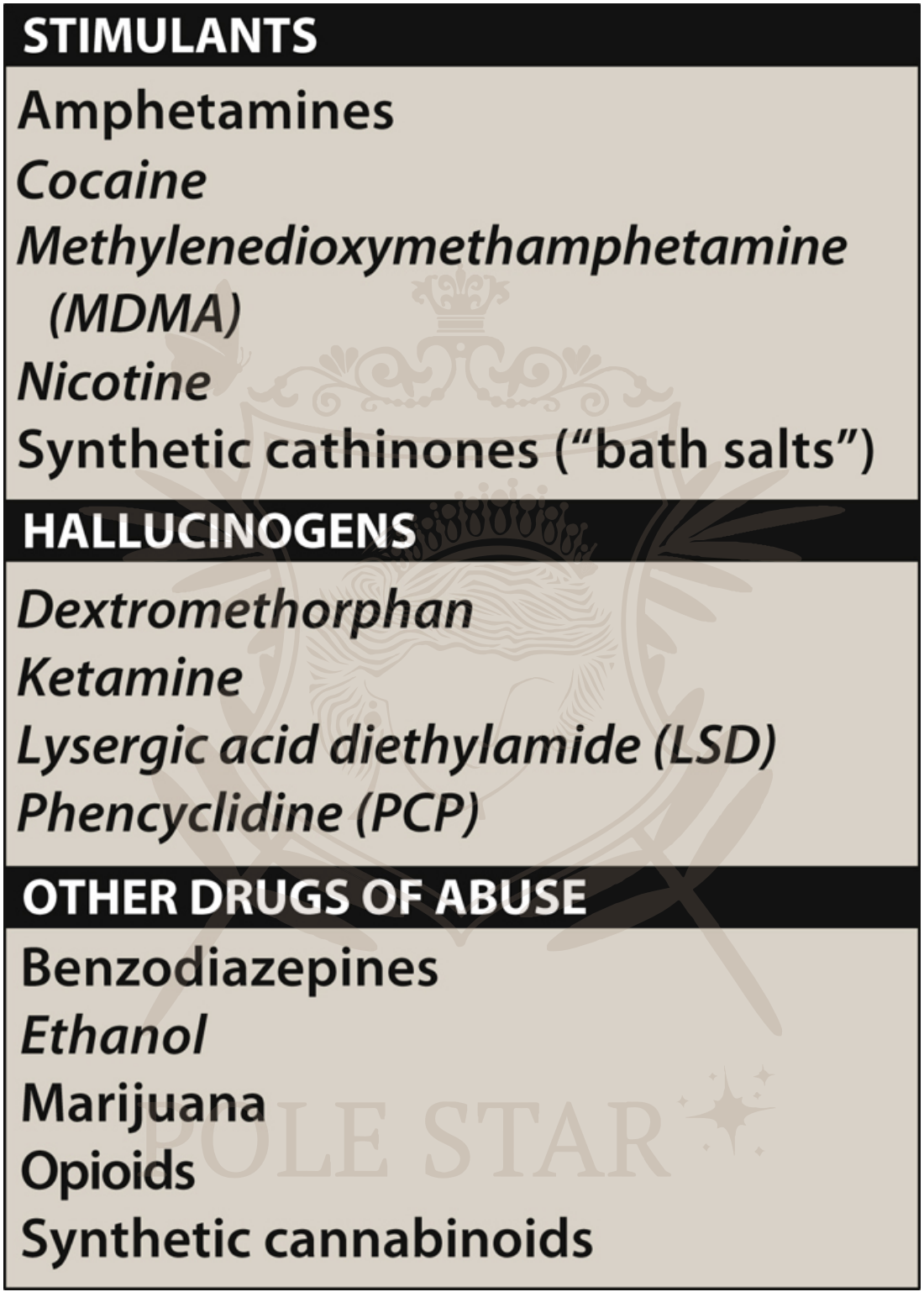

Figure 47.1 Summary of commonly abused substances.

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Substance use disorders occur in many forms, and their effects have been witnessed throughout the history of the world. The lure of addictive substances continues to impact people today. In 2020, approximately 21.4% of the population in the United States used some form of illicit substance (Figure 47.2), while 7.3% were considered to have an alcohol use disorder and 6.6% misused prescription medications. Abused substances have become progressively more potent, and their routes of administration have become increasingly effective, resulting in greater risks of addiction (Figure 47.3) and toxicity. Some examples of the methods, mechanisms, and clinical manifestations of toxicity of commonly abused substances are discussed in this chapter.

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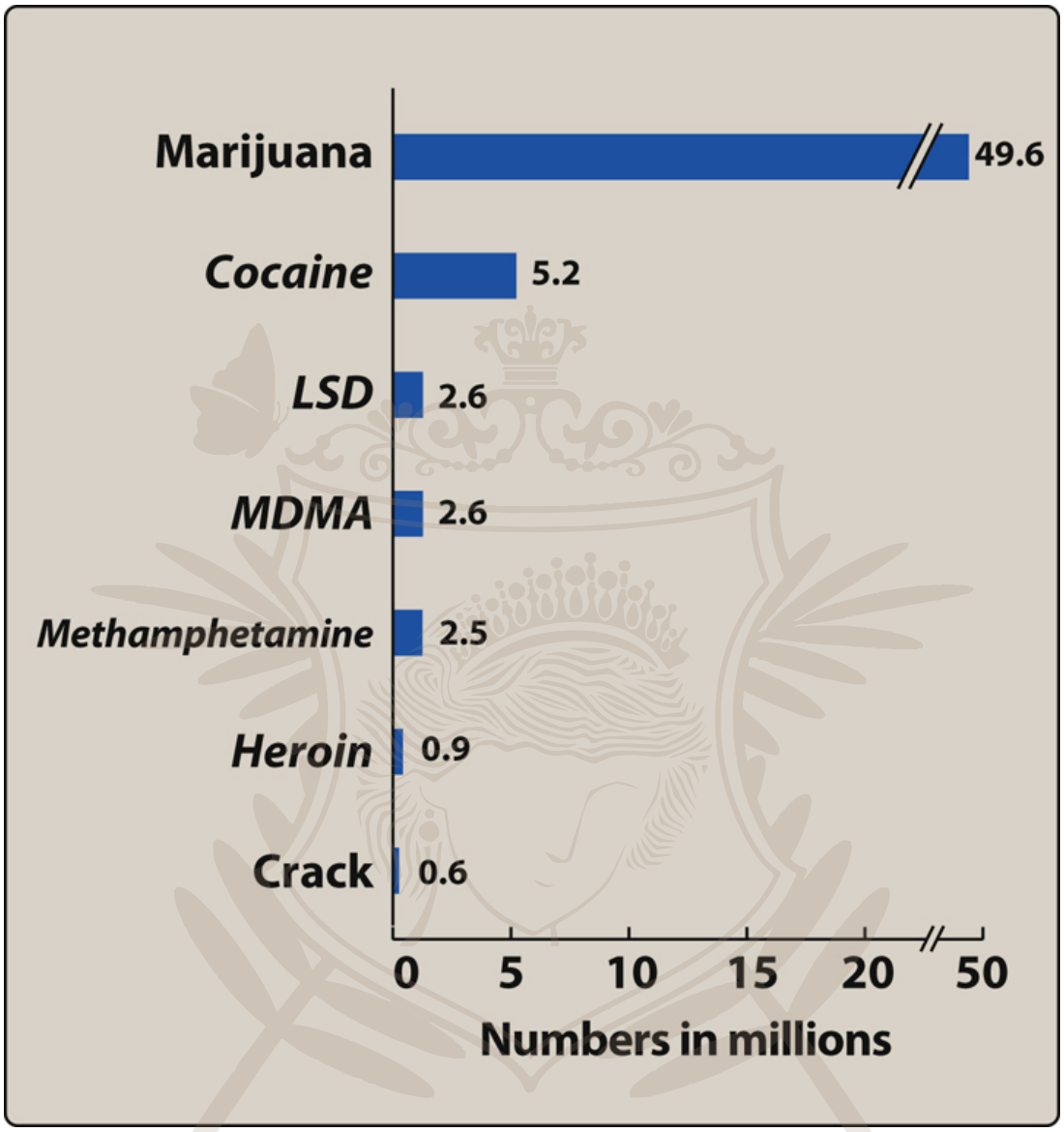

Figure 47.2 Past-year illicit drug use among persons aged 12 years or older in the United States.LSD = *lysergic acid diethylamide*; MDMA = *methylenedioxymethamphetamine*.Data from Substance Abuse and Mental Health Services Administration. (2021). Key substance use and mental health indicators in the United States: Results from the 2020 National Survey on Drug Use and Health (HHS Publication No. PEP21-07-01-003, NSDUH Series H-56). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Available at https://www.samhsa.gov/data/.

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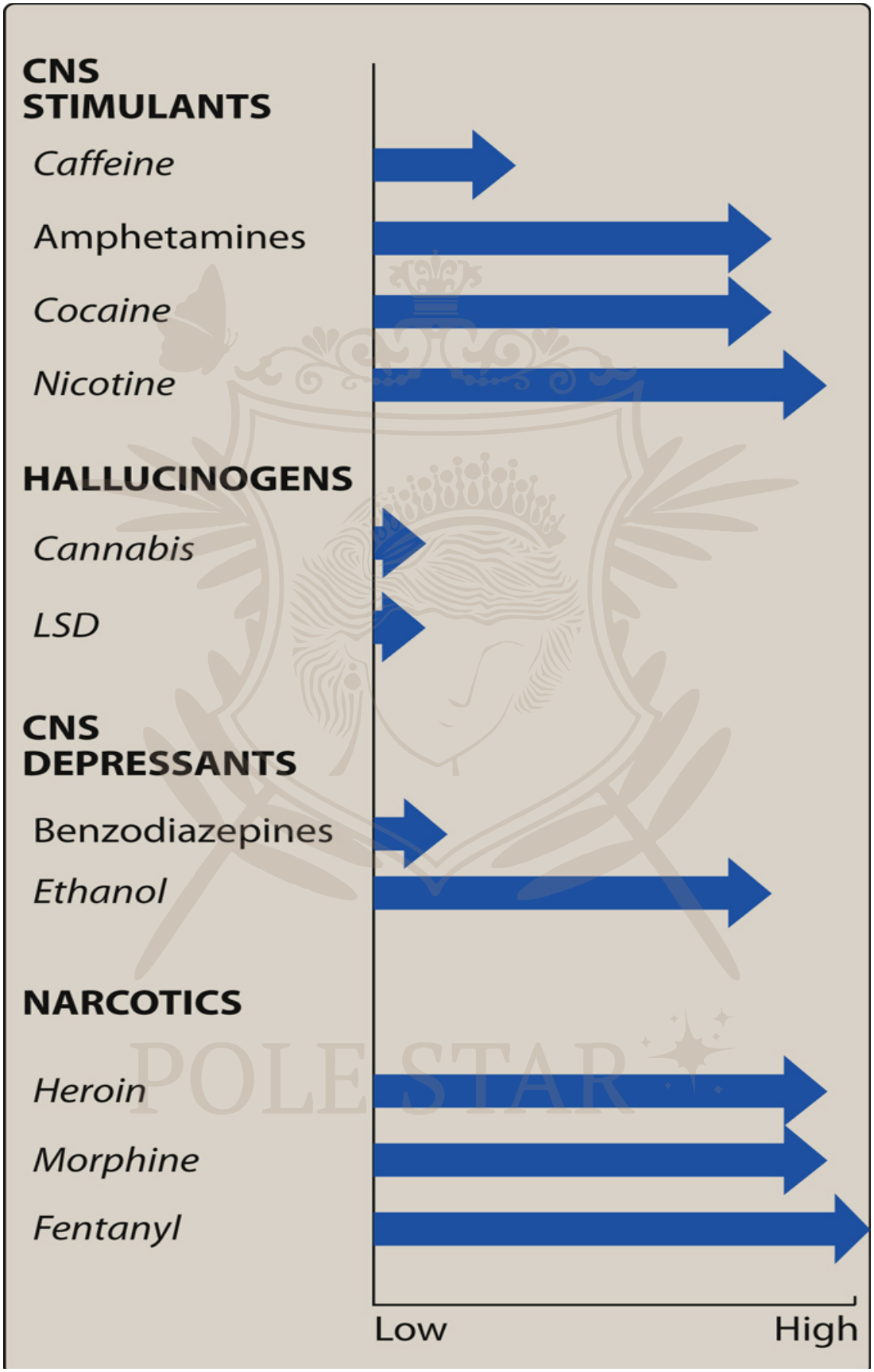

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Figure 47.3 Relative potential for physical dependence of commonly abused substances.

II. SYMPATHOMIMETICS

Sympathomimetics, such as *nicotine*, *cocaine*, and *amphetamine*, are stimulants that mimic the sympathetic nervous system, producing "fight-or-flight" responses. Sympathomimetics usually produce a relative increase of adrenergic neurotransmitters at the site of action (Figure 47.4), thereby causing hyperadrenergic effects such as tachycardia, hypertension, hyperthermia, and tachypnea. These agents come from natural sources, such as plants, or are synthesized in legitimate or clandestine laboratories. Aside from the stimulant effect, many of these agents have a remarkable ability to produce pleasure. Consequently, their addictive potential is great, and use for many of the agents continues to rise. One of the most commonly used and easily accessible sympathomimetics is *nicotine* (see Chapter 22).

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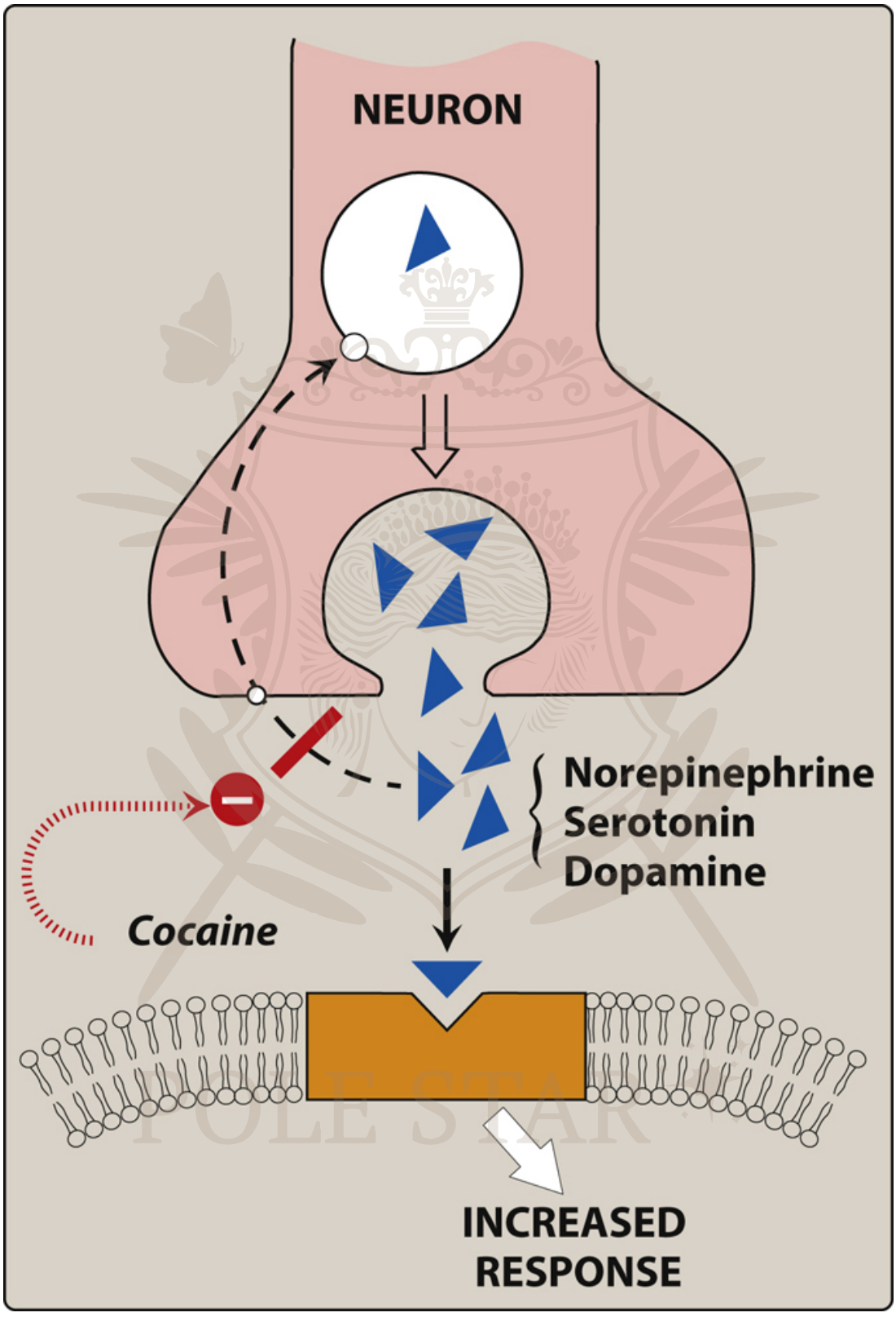

Figure 47.4 Mechanism of action of *cocaine*.

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A. Cocaine

Cocaine is derived from the coca shrub (Erythroxylum coca) that grows in the foothills of the Andes Mountains in South America.

1. Actions: *Cocaine* inhibits the transporters that recover norepinephrine, dopamine, and serotonin, thus increasing the availability of these neurotransmitters at the synapse. It causes central nervous system (CNS) stimulation by inhibiting the reuptake of norepinephrine into the adrenergic neuron. The profound ability of *cocaine* to stimulate the pleasure center of the human brain is thought to result from inhibition of reuptake of dopamine and serotonin.

2. Route of administration: *Cocaine* has minimal bioavailability when taken by the oral route. Instead, the *cocaine* hydrochloride powder is snorted or solubilized and injected. The *cocaine* powder cannot be effectively smoked, as it is destroyed upon heating. However, crack *cocaine*, an alkaloidal form, can be smoked. Smoking is an extremely effective route of administration, as the lungs are richly perfused with blood and carry the drug within seconds to its site of action, the brain. This causes an immediate, intense euphoria or "rush" that is followed rapidly by a strong sense of dysphoria or "crash." It is this immediate positive reinforcement, followed quickly by the negative reinforcement that makes the drug, particularly in this form, so addictive. Since *cocaine* products are often purchased by weight, street *cocaine* powder and crack are often adulterated with other drugs to increase the bulk amount of powder, mimic the action of *cocaine*, and thereby increase the profitability.

3. Toxicity: The clinical manifestations of *cocaine* toxicity are a function of its stimulant effects. Common reasons for *cocaine* users to present to the emergency department include psychiatric complaints (depression precipitated by *cocaine* dysphoria, agitation/paranoia), convulsions, hyperthermia, and

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chest pain. Hyperthermia is caused by *cocaine*-induced CNS stimulation that increases heat production and vasoconstrictive effects of *cocaine* that minimize the ability to dissipate heat. *Cocaine*-related chest pain can be chest muscle pain or cardiac in nature, as *cocaine* causes vasoconstriction of coronary arteries and accelerates the atherosclerotic process. Commonly, *cocaine* is consumed with *ethanol*, which creates a secondary metabolite cocaethylene. The metabolite is cardiotoxic and further contributes to cardiac issues related to *cocaine* consumption. *Cocaine* chest pain can also be related to pulmonary damage caused by inhalation of this heated impure substance. *Cocaine* convulsions are an extension of the CNS stimulant effect (Figure 47.5). *Cocaine* toxicity is treated by calming and cooling the patient. Benzodiazepines, such as *lorazepam* (see Chapter 16), help to calm the agitated patient and can both prevent and treat convulsions. In addition, the calming effect helps cool the patient and manage hyperthermia. This is an important therapeutic effect, as hyperthermia is one of the major causes of *cocaine* fatalities. The remainder of *cocaine* toxicity is treated with short-acting antihypertensives, anticonvulsants, and symptomatic supportive care.

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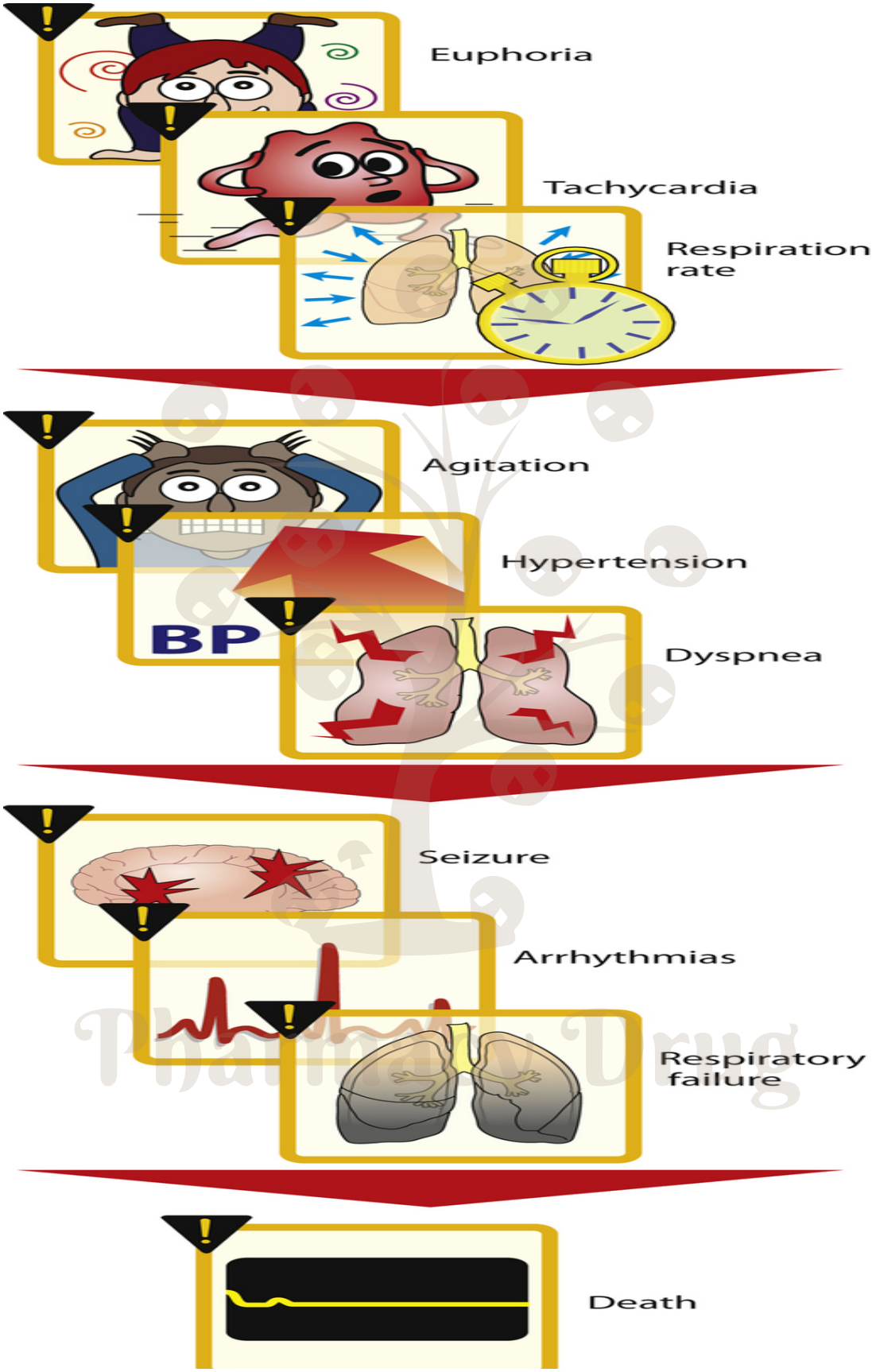

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Figure 47.5 Major effects of *cocaine* use.

B. Amphetamines

Amphetamines act by enhancing the release of biogenic amines from the storage sites in the nerve terminals, and they also inhibit neurotransmitter reuptake, leading to increased concentrations of neurotransmitters in the synaptic cleft. Amphetamines such as *methamphetamine* are sympathomimetics with clinical effects similar to those of *cocaine.* Clinical manifestations of *methamphetamine* use may also include teeth grinding (bruxism), itching and skin picking, and a dry mouth leading to significant tooth decay. In many cases, these effects may last longer and are associated with more stimulation and less euphoria when compared with *cocaine.* Treatment of *amphetamine* toxicity is similar to that of *cocaine* toxicity. Therapeutic uses of amphetamines are presented in Chapter 22.

C. Methylenedioxymethamphetamine

Methylenedioxymethamphetamine (*MDMA*), commonly known as ecstasy or Molly, is a hallucinogenic amphetamine with profound serotonin-releasing effects (Figure 47.6). It also enhances the activity of norepinephrine and, to a lesser extent, dopamine. Because of its unique serotonin properties, *MDMA* is sometimes referred to as an "empathogen," and tactile stimulation is particularly pleasurable to users. Many users of MDMA describe a sense of well-being and social interactivity. Like many amphetamines, *MDMA* can cause bruxism and trismus (jaw clenching). Misuse of *MDMA* can cause profound hyperthermia, altered mental status, and serotonin syndrome. Benzodiazepines help to calm and cool the patient. Life-threatening hyperthermia may require treatment with neuromuscular blockers and endotracheal intubation to control excessive movement and heat generation. *Cyproheptadine* is a serotonin antagonist that has been used to treat serotonin syndrome; however, one of its

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practical limitations is that it is only available in an oral formulation. [Note: *MDMA* products are often adulterated with other drugs such as *methamphetamine*, *ketamine*, or *methylone* (a synthetic cathinone; see below) which may be less expensive or easier to produce. The chemical structure of *methylone* differs from MDMA by one carbonyl group (Figure 47.7). Ingestion of an unknown combination of drugs in adulterated products may add to the serious risks of misuse of *MDMA*.]

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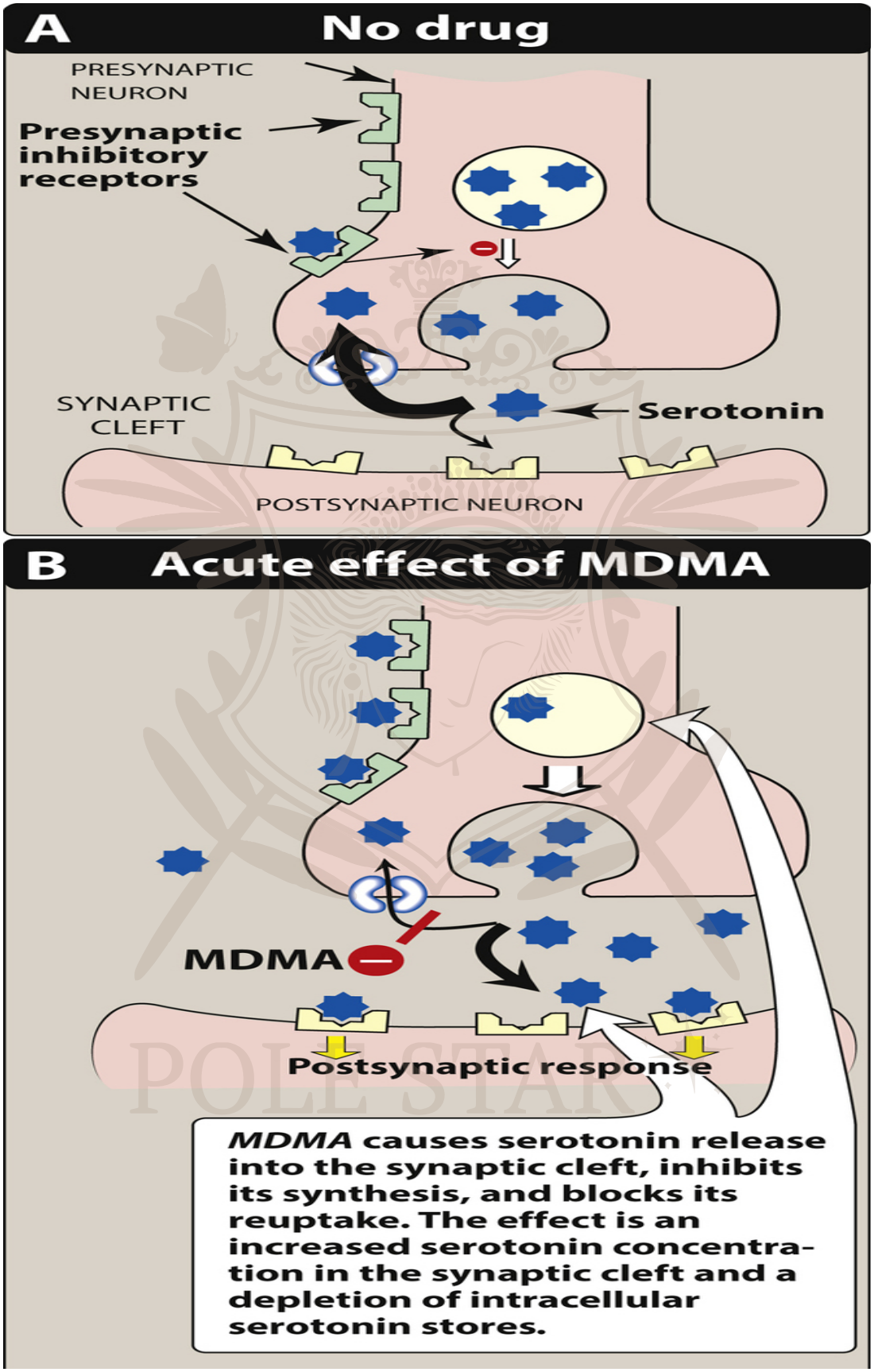
A
No drug
PRESYNAPTIC NEURON
Presynaptic inhibitory receptors
SYNAPTIC CLEFT
Serotonin
POSTSYNAPTIC NEURON
B
Acute effect of MDMA
MDMA
Postsynaptic response
MDMA causes serotonin release into the synaptic cleft, inhibits its synthesis, and blocks its reuptake. The effect is an increased serotonin concentration in the synaptic cleft and a depletion of intracellular serotonin stores.

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Figure 47.6 Proposed mechanism of action of *methylenedioxymethamphetamine (MDMA)*.

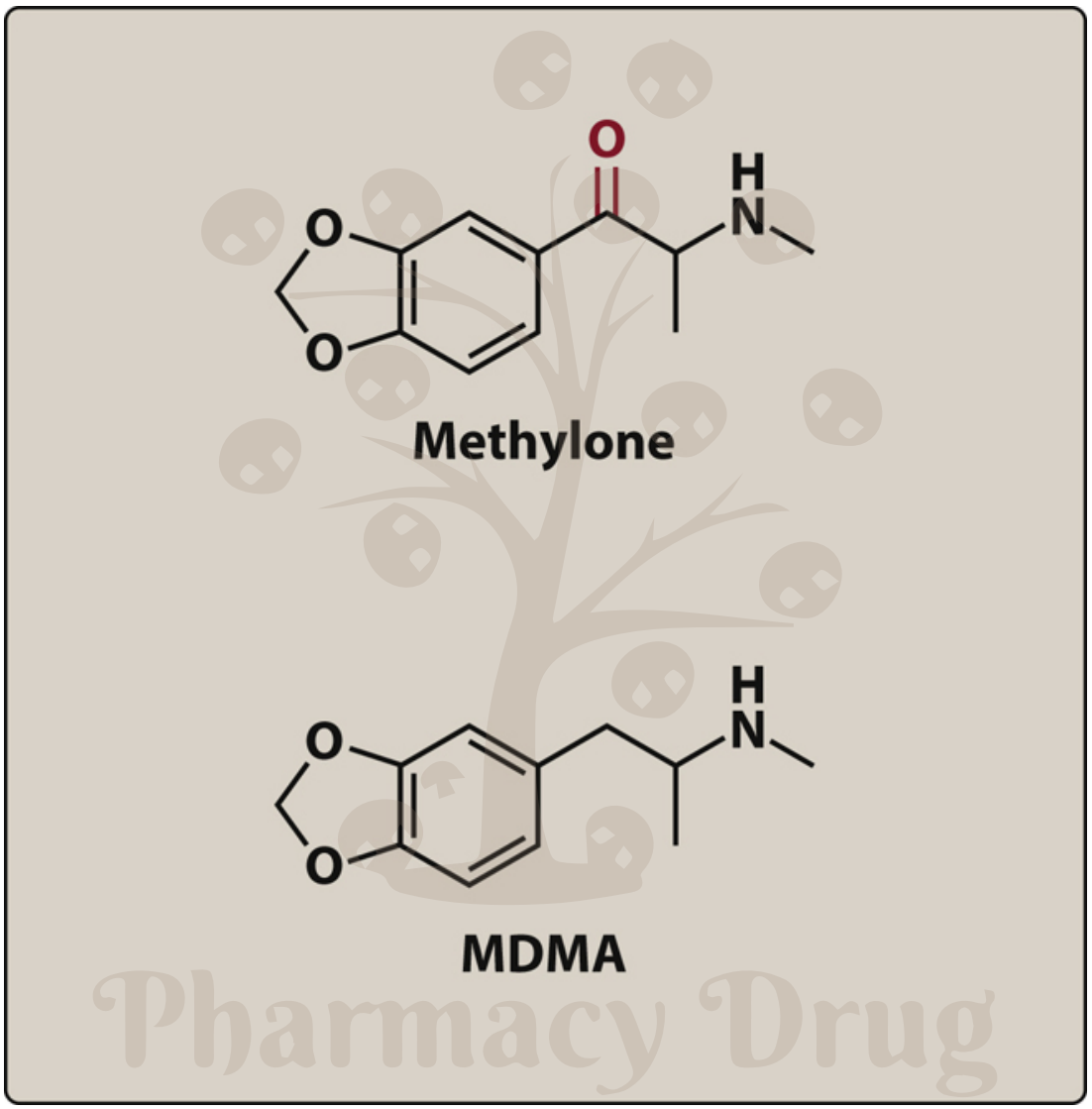

Figure 47.7 Comparison of the structures *of methylenedioxymethamphetamine* and *methylone*.

D. Synthetic cathinones

A L G r a w a n y

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Cathinone is the psychoactive component in the evergreen shrub Khat (Catha edulis) native to East Africa and the Arabian Peninsula. Synthetic cathinones (also known as "bath salts") are human-made substances that are chemically similar to cathinone. *Methylone, methcathinone*, 3,4-*methylenedioxypyrovalerone* (MDPV), and *mephedrone* are examples of synthetic cathinones. These drugs increase the release and inhibit the reuptake of catecholamines (norepinephrine, epinephrine, and dopamine) in a manner similar to *cocaine* and amphetamines. A rapid onset of *amphetamine*-like stimulation with psychotomimetic effects of variable duration is common with synthetic cathinones. These products are promoted as affordable alternatives to other stimulants and are often sold as "bath salts," "jewelry cleaner," or "plant food." The packages are labeled "not for human consumption" to circumvent detection, prosecution, and enforcement. Bath salts are generally snorted or ingested, but they may also be injected. Synthetic cathinones are not easily detected in urine toxicology screens. Treatment of toxicity is similar to the emergent treatment of amphetamines and *cocaine*.

Clinical Application 47.1: Management of Stimulant Toxicity

A 25-year-old man who has been misusing sympathomimetic stimulants arrives in the emergency department agitated, tachycardic, hypertensive, and hyperthermic. The major life-threatening acute concerns include convulsions, cardiac arrhythmias, myocardial infarction, neurological events (ischemia or hemorrhagic stroke), and profound hyperthermia, as well as combative and/or self-destructive behavior. Initial treatment should include calming the patient and providing prophylactic treatment against convulsions, including benzodiazepines, cooling measures, and additional symptomatic/supportive care. Depending on the stimulants ingested, serotonin syndrome might be suspected and the addition of *cyproheptadine* may be considered.

III. HALLUCINOGENS

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Hallucinogens (also called psychedelics) are drugs that can alter perceptions of reality, as well as individual thoughts and feelings. This category of agents includes classic hallucinogens, such as *D-lysergic acid diethylamide*, and dissociative hallucinogens, such as *phencyclidine*.

A. D-lysergic acid diethylamide

D-lysergic acid diethylamide (LSD), is perhaps the most commonly recognized drug in the hallucinogen class. *LSD* was first created from ergot, a fungus that grows on rye and other grains, in 1938 by Dr. Albert Hoffman. *LSD* produces psychedelic effects through serving as a potent partial agonist at 5-HT_{2A} receptors. It commonly causes increased perceptions of sensory input, a distorted sense of time, and a blending of senses, where users may "hear" colors or "see" sounds. Aside from colorful hallucinations, the drug is also responsible for mood alterations, sleep disturbances, and anxiety. Repeated use rapidly produces tolerance through downregulation of serotonin receptors. *LSD* may be administered via blotter paper (small sheets of paper soaked with drugs that are absorbed via the lining of the mouth), liquid, or pills.

Although physical adverse effects are typically minimal, *LSD* may cause mydriasis, tachycardia, increased blood pressure and temperature, dizziness, decreased appetite, and sweating. In addition, loss of judgment and impaired reasoning are associated with use of *LSD.* Use sometimes results in feelings of extreme panic, which may lead to trauma. Flashbacks may also occur, in which an individual may experience a recurrence of symptoms months or years after their last use of the drug.

B. Dissociative hallucinogens

Dissociative hallucinogens result in perceptions of detachment from the current environment and self (depersonalization), causing users to feel disconnected and out of control of their body. Agents in this category include *phencyclidine* (*PCP*),

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ketamine, and *dextromethorphan. PCP* (also known as "angel dust") was originally developed for use as an anesthetic in the 1950s; however, due to significant adverse effects, such as agitation, hallucinations, and postoperative dysphoria, use for this purpose was soon discontinued. It became a drug of abuse due to its hallucinogenic properties and ability to cause a sense of depersonalization. While use of *PCP* has declined significantly, the use of *ketamine* has risen, perhaps due to its availability as an approved drug product. *Ketamine* is approved for use as an anesthetic in human and veterinary medicine (see Chapter 20). It is used illicitly, since it causes a dream-like state and hallucinations similar to *PCP.* Both *PCP* and *ketamine* are N-methyl-D-aspartate (NMDA) receptor antagonists. *Dextromethorphan* is an antitussive compound available in many nonprescription cough medications (see Chapter 41). In addition to blocking the medullary cough center reflex, it also blocks NMDA receptors in the central nervous system. In low doses, *dextromethorphan* has a low addictive profile; however, with misuse it can cause hallucinations and euphoria.

C. Other hallucinogens

A group of synthetic serotonin agonists collectively known as "N-Bomb" have been substituted for *LSD.* Like *LSD*, these agents are used in liquid form or with blotter paper and have resulted in hypertension, convulsions, and accidental traumatic injury and death. *Mescaline* (from the peyote cactus) and *psilocybin* (also known as magic mushrooms) are also common hallucinogens that produce neuropsychiatric effects similar to *LSD*.

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IV. CANNABIS (MARIJUANA)

Cannabis is a plant that has been used by humans for over 10,000 years. Centuries-old Chinese documents describe the use of cannabis for clothing production and food and as an agent to communicate with spirits. Certain cannabis plants can be used for

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making rope or clothing; however, the species Cannabis sativa is the plant most often used for its psychoactive properties.

A. Marijuana

Marijuana refers to the parts of the Cannabis plant that contain substantial amounts of the main psychoactive alkaloid, Δ^9-*tetrahydrocannabinol* [tet-ra-HY-dro-can-NAB-i-nol] (*THC*). Although marijuana contains dozens of components, the most commonly recognized are *THC* and *cannabidiol* (*CBD*). Growing techniques for marijuana have evolved over the past 60 years, and *THC* concentrations found in the plant have increased as much as 20-fold during that time. Today, marijuana is a drug commonly used for both illicit and medicinal purposes and the illicit drug that new users are most likely to try (Figure 47.8). Those numbers are expected to grow as liberalization of marijuana laws continue in many countries.

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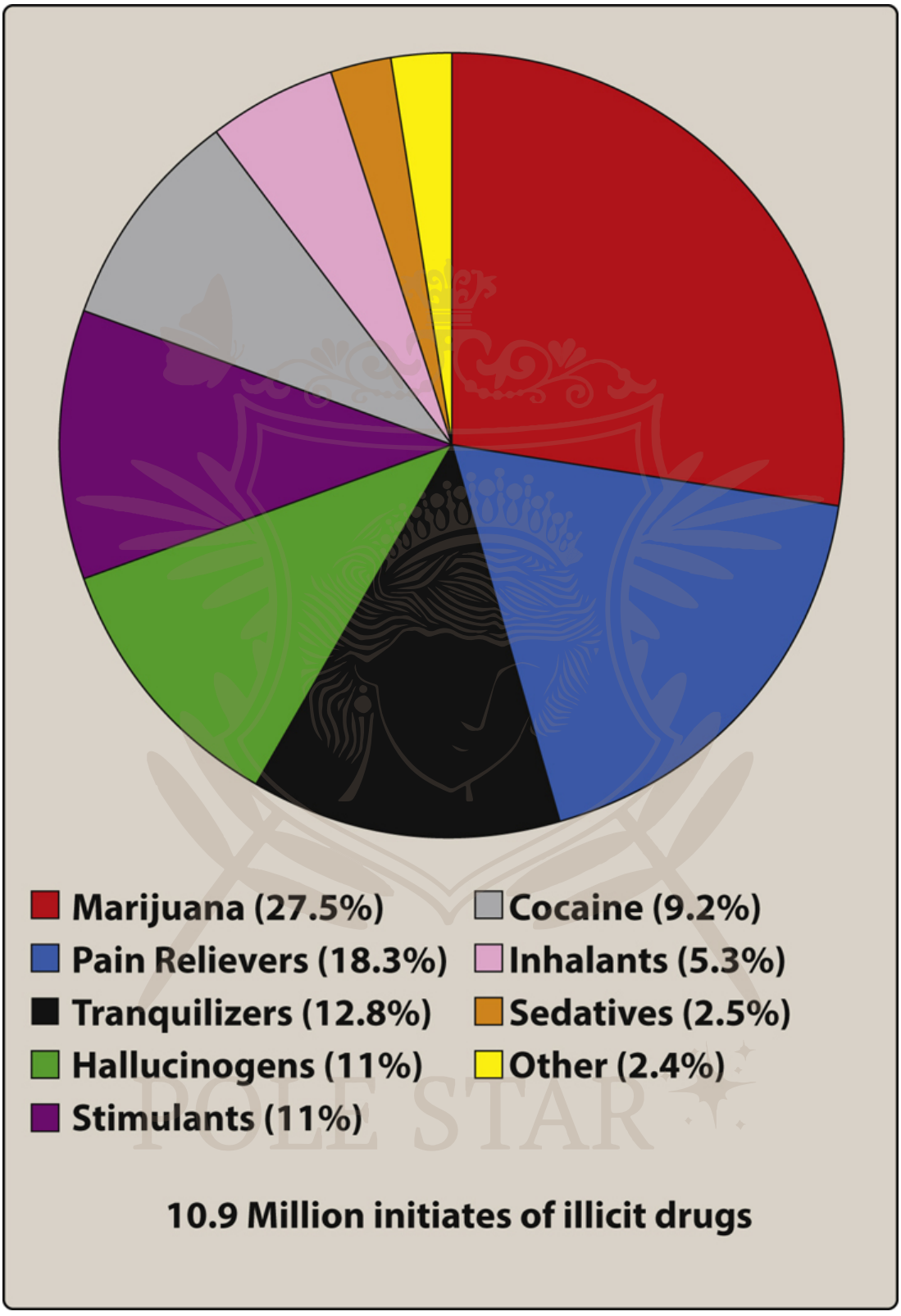
Marijuana (27.5%)
Pain Relievers (18.3%)
Tranquilizers (12.8%)
Hallucinogens (11%)
Stimulants (11%)
Cocaine (9.2%)
Inhalants (5.3%)
Sedatives (2.5%)
Other (2.4%)
10.9 Million initiates of illicit drugs

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Figure 47.8 Specific drug associated with initiation of illicit drug use among past-year illicit drug initiates aged 12 years or older.

1.Actions: Specific receptors in the brain, cannabinoid or CB_1 receptors, were discovered in the late 1980s and found to be reactive to *THC.* When CB_1 receptors are activated by marijuana, effects include physical relaxation, hyperphagia (increased appetite), increased heart rate, decreased muscle coordination, conjunctivitis, and minor pain control (Figure 47.9). Depending on the social situation, *THC* can produce euphoria, followed by drowsiness and relaxation. Although hallucinations are typically not as robust as those observed with use of *LSD*, marijuana is often used for the mild hallucinogenic effects that it produces.

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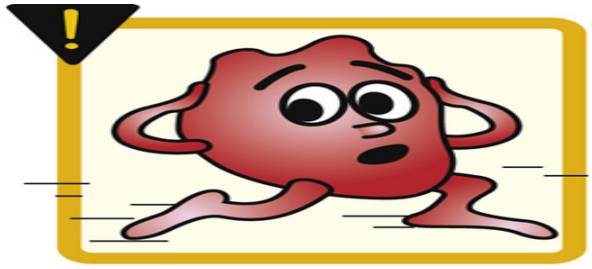
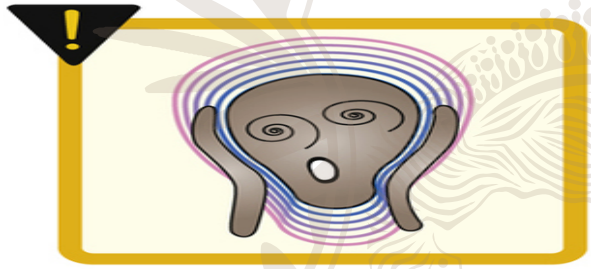
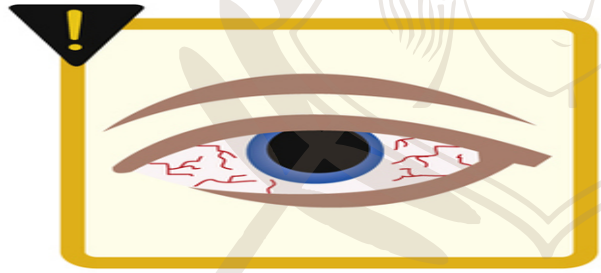


Tachycardia

Impaired memory



Hallucinations



Conjunctivitis

Increased appetite

Impaired coordination

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Figure 47.9 Effects of *tetrahydrocannabinol*.

2.Therapeutic uses: *CBD* is the component of marijuana most often used for its potential medical benefits including seizure disorders and pain and spasticity associated with multiple sclerosis. It does not produce the euphoric effect that is associated with *THC.* Although not well studied for medicinal use, marijuana has been used as an adjuvant in the treatment of chemotherapy-induced nausea and vomiting (CINV), cachexia secondary to cancer and AIDS, epilepsy, chronic pain, multiple sclerosis, glaucoma, and anxiety.

3.Route of administration: Marijuana is smoked in various forms (cigarettes, water pipes, pipes, or blunts), inhaled via a vaporizer, ingested in foods such as cookies or candy, or consumed in brewed beverages (for example, tea). The effects of *THC* appear immediately after smoking marijuana, but maximum effects take about 20 minutes. By 3 hours, the effects largely disappear.

4.Adverse effects: Marijuana stimulates the amygdala, causing the user to have a sense of novelty to anything the user encounters through an enhancement of sensory activity. For this same reason, heavy users have a downregulation in CB_1 receptors, leaving them with a feeling of boredom when not taking the drug. The effects of marijuana on γ-aminobutyric acid (GABA) in the hippocampus diminish the capacity for short-term memory in users, and this effect seems to be more pronounced in adolescents. In addition to adversely affecting short-term memory and mental activity, *THC* decreases muscle strength and impairs highly skilled motor activity, such as that required to drive a car. Heart rate is elevated after smoking marijuana, and there may be an increased risk of myocardial infarction in the first hour after marijuana use.

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Adverse effects in chronic users may include cough, lung infections, cannabinoid-induced hyperemesis syndrome (Figure 47.10), and a decline in cognitive function. Tolerance develops rapidly; 9% of all users and 17% of adolescent users develop dependence, and withdrawal has been observed. Marijuana may be found in the body up to 3 months after last usage in heavy chronic users. For this reason, withdrawal occurs much later in individuals who previously used marijuana heavily. Withdrawal may include cravings, insomnia, depression, pain, and irritability.

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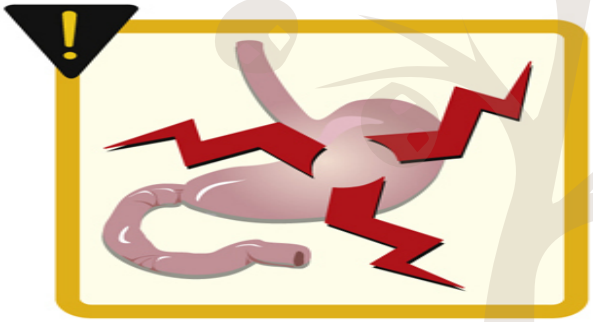
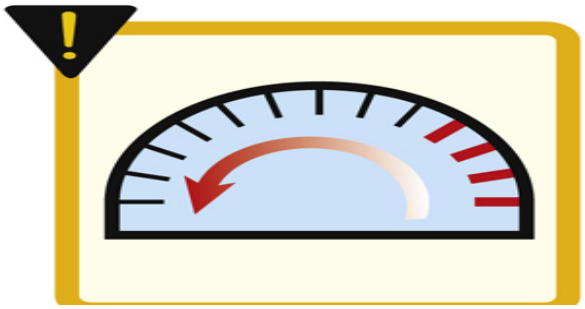
Nausea

Severe vomiting and/or diarrhea



Stomach pain

Use of hot showers for relief



Weight loss

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Figure 47.10 Symptoms of cannabinoid hyperemesis syndrome.

B. Synthetic THC derivatives

Synthetic *THC* medications are available as prescription products and include *dronabinol* [droe-NAB-i-nol] and *nabilone* [NA-bi-lone]. These medications are used for the prevention of CINV. *Nabiximols* (not available in the United States), a medication created from the extract of the C. sativa plant, is an oromucosal spray available in several countries throughout the world for the treatment of spasticity in multiple sclerosis.

C. Synthetic cannabinoids

Synthetic cannabinoids are sprayed onto plant material in a process known as dusting. These products such as "Spice" and "K2" are then smoked or ingested in tea to produce intoxication. Since the molecular structure of synthetic cannabinoids is much different from the cannabinoids found in marijuana plants, users do not test positive for *THC* with traditional drug tests. Sympathomimetic effects may also be seen in users, including tachycardia and hypertension. The greatest danger with use of these agents includes extreme hallucinations and psychotic reactions. Formulations of synthetic cannabinoids and their contaminants have caused convulsions, acute kidney injury, and death.

V. ETHANOL AND AGENTS FOR TREATMENT OF ALCOHOL DEPENDENCE

Ethanol is the most commonly abused substance in modern society, with the prevalence of alcohol use disorder as high as 12.6% of the population in some regions of the world.

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A. Ethanol

Ethanol (or alcohol) is a clear colorless hydroxylated hydrocarbon that is the product of fermentation of fruits, grains, or vegetables. *Ethanol* consumption is a major cause of deadly automobile accidents, drownings, and fatal falls and is a related factor in many hospital admissions. Alcohol use disorder decreases life expectancy by 10 to 15 years and impacts one in three families.

1.Actions: It is thought that *ethanol* exerts its desired and toxic effects through several mechanisms, including enhanced effects of the inhibitory neurotransmitter GABA, increased release of endogenous opioids, and altered levels of serotonin and dopamine. Its sedative and anxiolytic effects are likely related to its effect on the $GABA_A$ receptor. There is also evidence that it affects the NMDA receptor, which may have a role in the tolerance, dependence, and withdrawal syndrome associated with alcohol. *Ethanol* is a selective CNS depressant at low doses, resulting in decreased inhibition and the characteristic increase in social behavior and impulsivity. At high doses, it is a general CNS depressant, which can result in coma and respiratory depression.

2.Pharmacokinetics: Drinking *ethanol* traditionally has been the most common route of administration. *Ethanol* is absorbed from the stomach and duodenum, and food slows and decreases absorption. Peak *ethanol* levels are generally achieved within 20 minutes to 1 hour of ingestion. There is a greater subjective feeling of intoxication while levels are ascending (absorption), as compared with when levels are descending. *Ethanol* is metabolized by alcohol dehydrogenase to acetaldehyde and then by aldehyde dehydrogenase to acetate in the liver (Figure 47.11). It is metabolized by zero-order elimination at approximately 15 to 40 mg/dL/h. Because there is a constant blood-to-breath ratio of 2100:1, a breath sample can be used to determine blood alcohol levels. Medical management of acute *ethanol* toxicity includes symptomatic

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supportive care and thiamine and folate administration. Patients with extremely high alcohol levels can be dialyzed, although that is rarely necessary and could precipitate withdrawal in an individual with alcohol use disorder.

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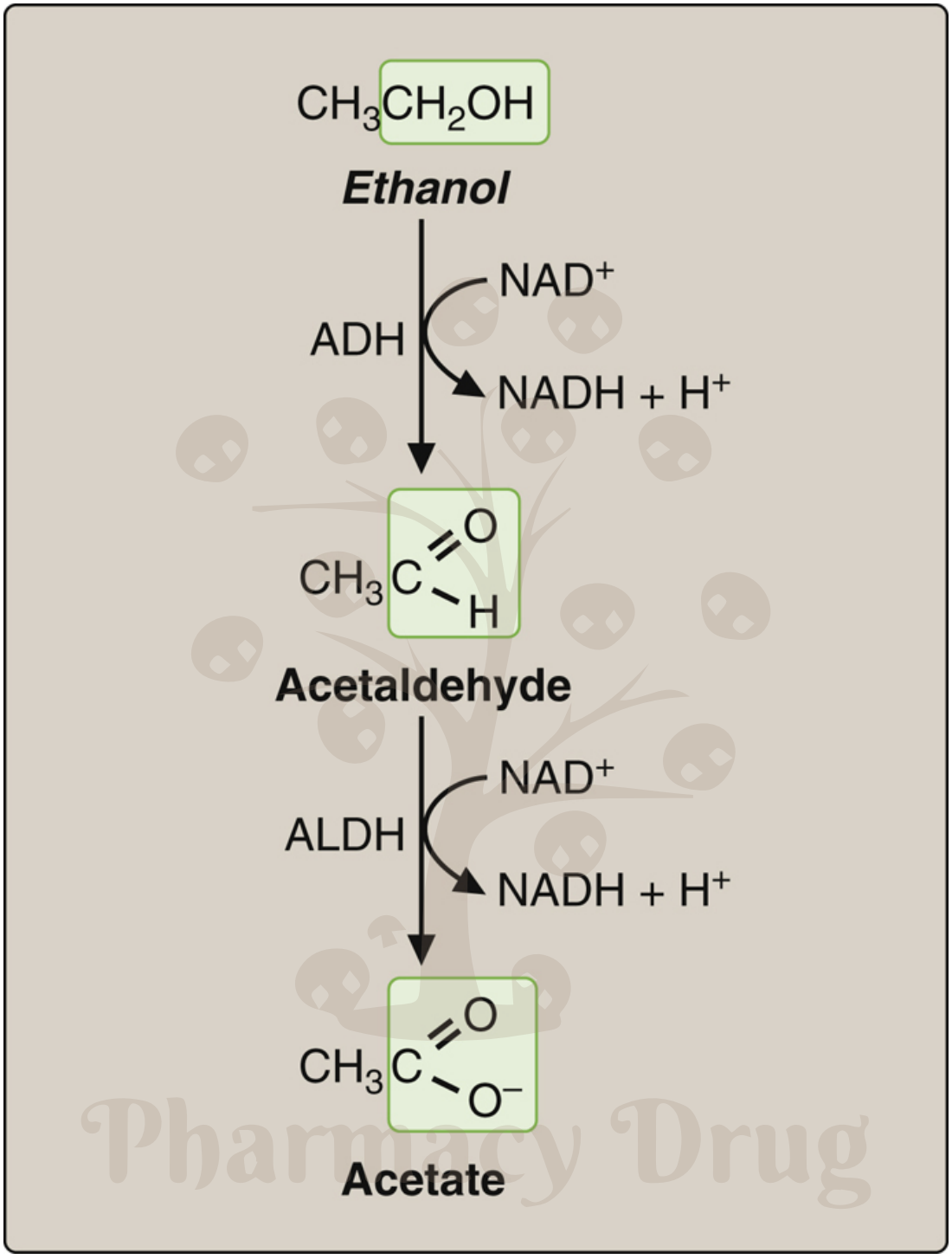

Figure 47.11 The pathway of *ethanol* metabolism.ADH = alcohol dehydrogenase; ALDH = acetaldehyde dehydrogenase.

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3.Adverse effects: Chronic *ethanol* misuse can cause profound hepatic, cardiovascular, pulmonary, hematologic, endocrine, metabolic, and CNS damage (Figure 47.12). Sudden cessation of *ethanol* ingestion in someone with severe alcohol use disorder can precipitate withdrawal manifested by tachycardia, sweating, tremor, anxiety, agitation, hallucinations, and convulsions. Delirium tremens is the most severe form of withdrawal, which can lead to mental status changes, hallucinations, and autonomic instability (hyperactivity) that may lead to cardiovascular collapse. Alcohol withdrawal can be a life-threatening situation that should be medically managed with symptomatic/supportive care, benzodiazepines, and long-term treatment for alcohol use disorder.

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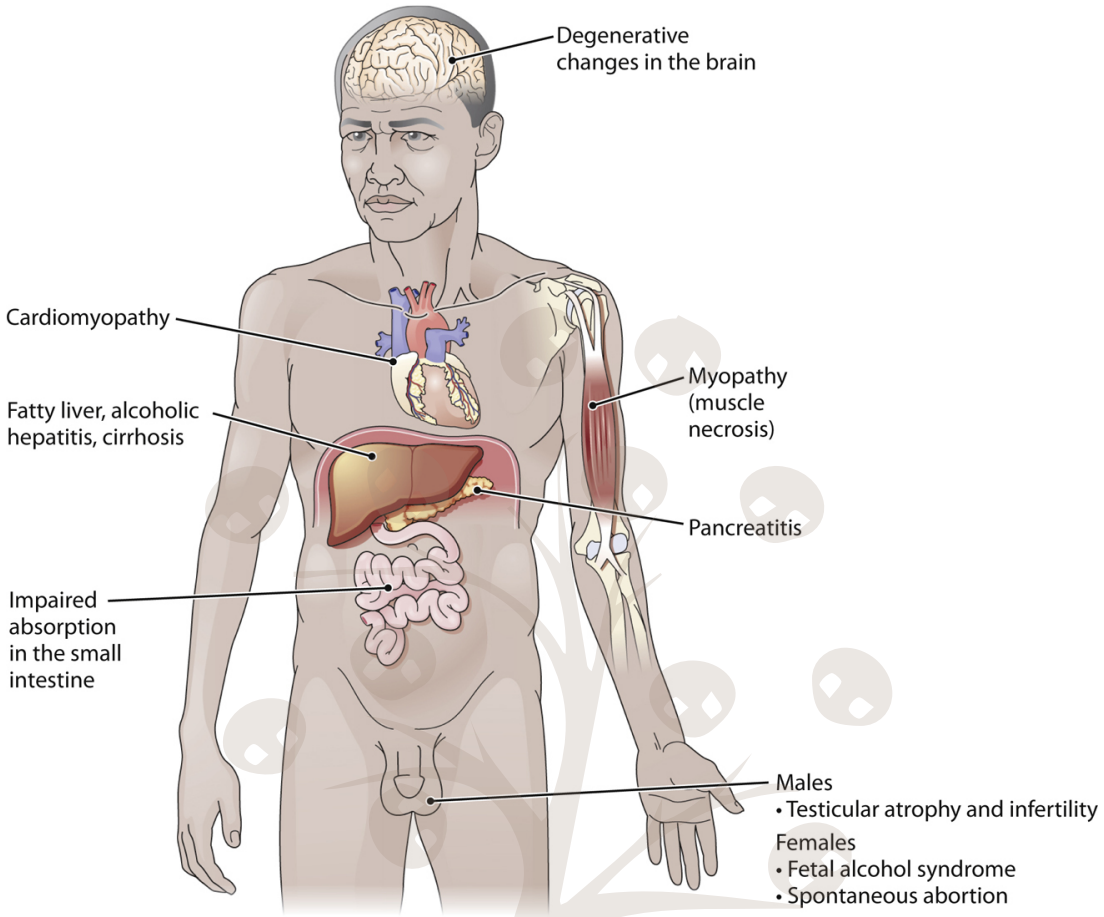

Figure 47.12 The effects of chronic alcohol abuse.

B. Drugs for alcohol dependence

Drugs for the treatment of alcohol dependence help patients maintain abstinence from *ethanol.* These agents should be used in conjunction with supportive psychotherapy. *Disulfiram* [dye-SUL-fi-ram] blocks the oxidation of acetaldehyde to acetic acid by inhibiting aldehyde dehydrogenase (Figure 47.13). If *ethanol* is ingested, it results in accumulation of acetaldehyde in the blood, causing flushing, tachycardia, hyperventilation, and nausea. A conditioned avoidance response is induced so that the patient abstains from alcohol to prevent the unpleasant effects of *disulfiram*-induced acetaldehyde accumulation. *Disulfiram* has found some use in patients motivated to stop alcohol ingestion.

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Naltrexone [nal-TREX-own] is a competitive and relatively long-acting opioid antagonist that helps decrease cravings for alcohol. *Naltrexone* is better tolerated than *disulfiram* and does not produce the aversive reaction that *disulfiram* does. *Acamprosate* [a-kam-PROE-sate] is thought to decrease cravings through its regulatory effects on NMDA-mediated glutamatergic excitation.

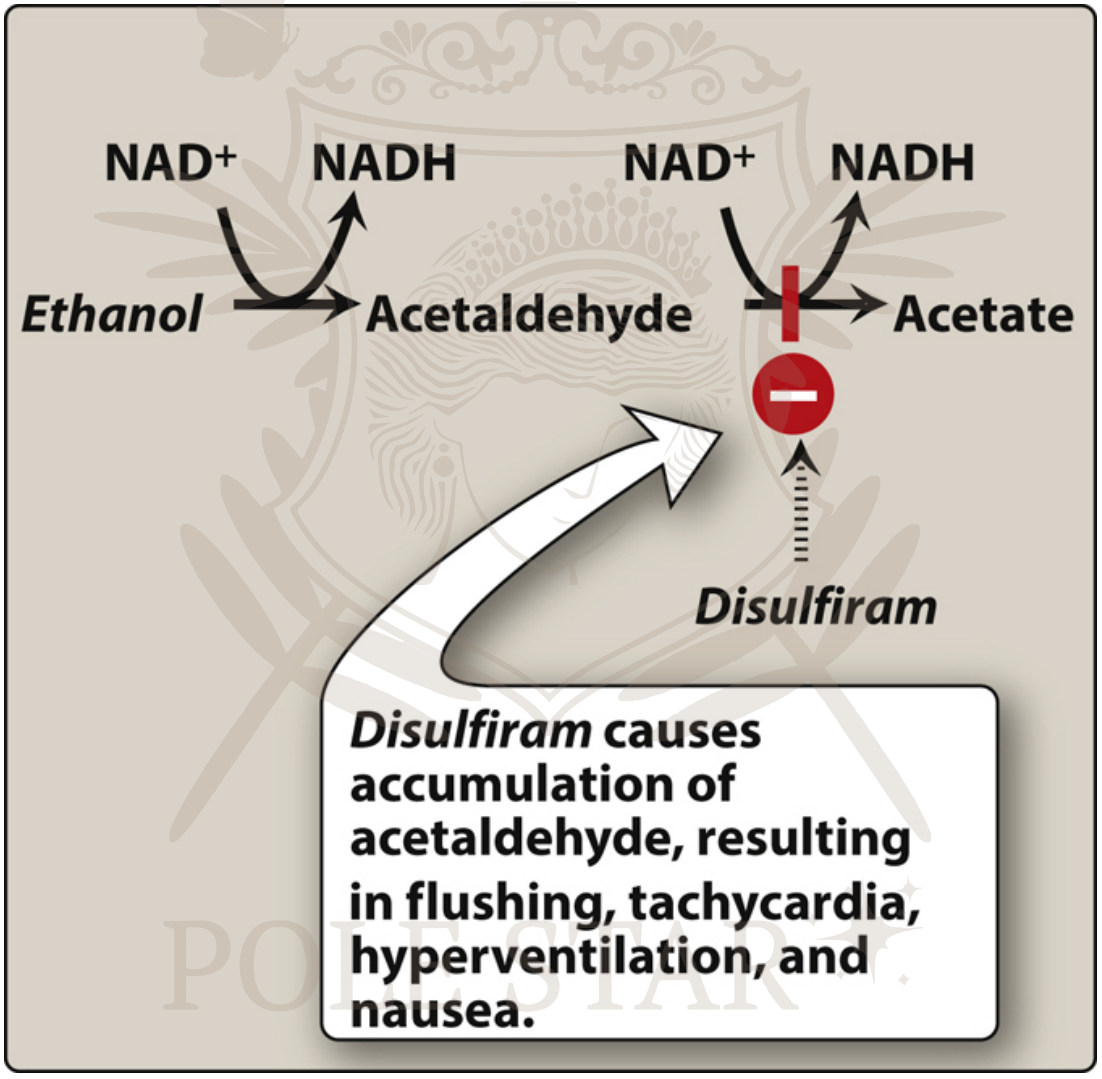

Figure 47.13 The effect of *disulfiram* on the metabolism of *ethanol*.

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Clinical Application 47.2 Management of Acute Ethanol Intoxication

A 56-year-old woman with a 35-year history of chronic alcohol misuse who has been drinking heavily arrives in the emergency department obtunded with borderline hypotension. Her initial blood alcohol level is 320 mg/dL. [Note: This blood alcohol level is four times the legal alcohol limit for driving an automobile in the United States.] Her history, obtundation, and blood pressure warrant close observation in the critical area of the emergency department. Initial treatment should include airway management as necessary, intravenous fluids, and symptomatic and supportive care.

Over the next 8 hours, she becomes progressively more alert, and eventually agitated and tachycardic. At this point, alcohol withdrawal becomes a concern. Subsequent treatment may include benzodiazepines acutely, followed by alcohol use disorder treatment in the long term.

VI. PRESCRIPTION DRUG MISUSE

This chapter has discussed many of the substances that are misused by individuals. In addition, many parts of the world, including the United States and portions of Europe, continue to experience an epidemic of prescription drug misuse. Some commonly misused prescription drugs include opioids and benzodiazepines. An increased emphasis on treating pain as the "fifth vital sign," coupled with an exaggerated belief in the beneficial capacity of these medications and a minimization of their inherent toxicity among the lay public and health professionals, was among the many possible explanations for the epidemic. Efforts have been made to decrease the misuse of prescription opioids, which has resulted in an increased use of *heroin* and *fentanyl*, often adulterated with extremely potent *fentanyl* derivatives such as *carfentanil.* Reversal of *fentanyl* and its derivatives is much more difficult than reversal of opioids such as *morphine.* This has contributed to a dramatic increase in death rates (Figure 47.14). Medications for the treatment of opioid toxicity and dependence are reviewed in Chapter 21.

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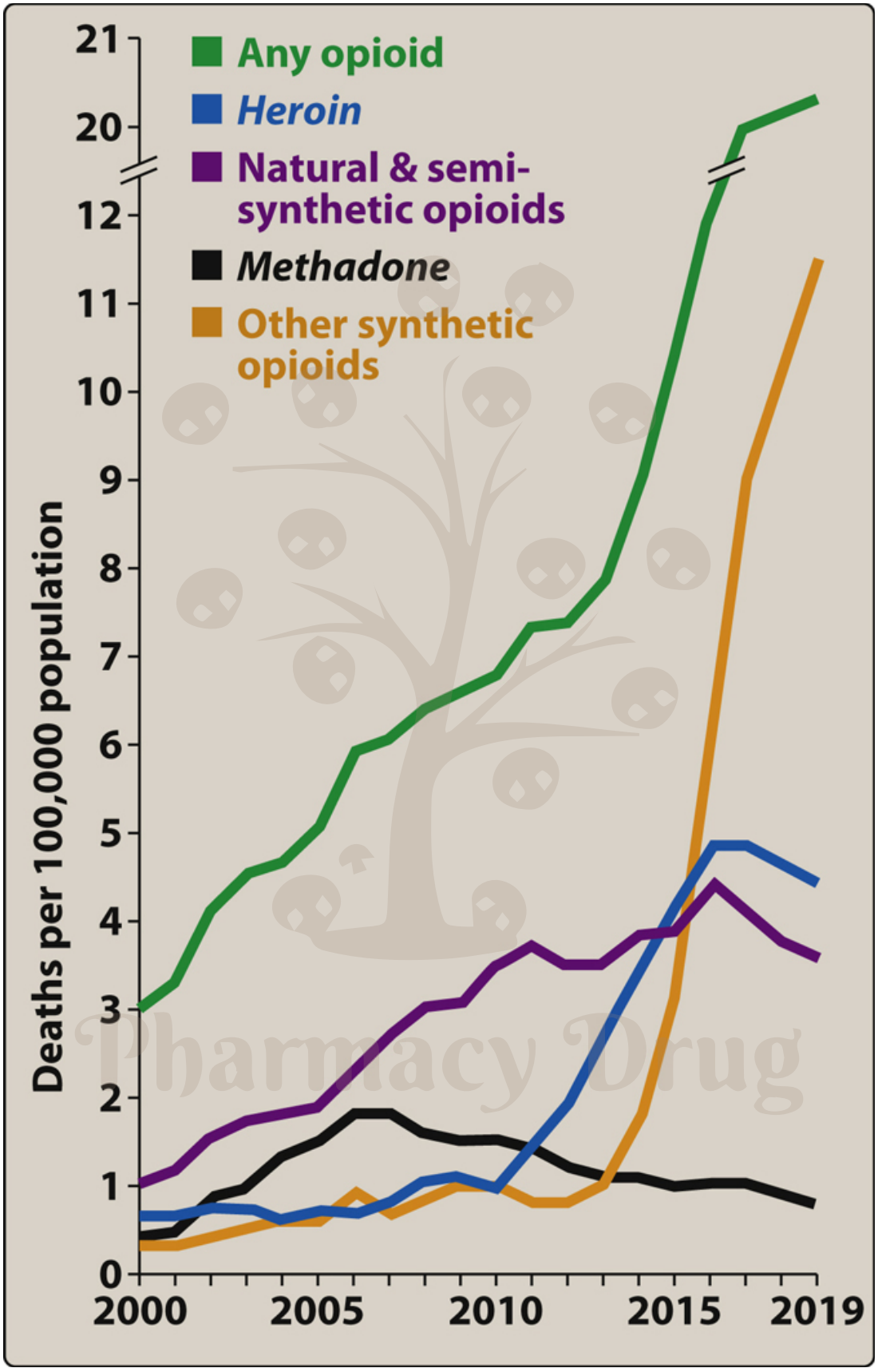

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Figure 47.14 Overdose deaths involving opioids in the United States between 2000 and 2019.Natural and semisynthetic opioids include *hydrocodone* and *oxycodone.* Other synthetic opioids include *fentanyl*, *fentanyl* derivatives, and *tramadol*.Source: From the Centers for Disease Control and Prevention; National Center for Health Statistics. *National Vital Statistics System, mortality. CDC WONDER*. Atlanta, GA, US Department of Health and Human Services, CDC (2020).

Chapter Summary

- Many drugs of abuse are sympathomimetics (*cocaine*, amphetamines, cathinones, etc.) and central nervous system (CNS) stimulation, tachycardia, hypertension, and hyperthermia are common and potentially severe toxic effects.
- Crack is a highly addictive, manufactured, alkaloidal form of *cocaine* that provides an extremely effective route of administration (smoking) with potent and rapid positive and negative reinforcement.
- Acute sympathomimetic toxicity is treated with benzodiazepines (for example, *lorazepam*, *diazepam*), cooling measures as necessary, and symptomatic supportive care.
- While *lysergic acid diethylamide (LSD*) can cause mild tachycardia and large, mydriatic pupils, physical effects are relatively minimal. However, trauma is a concern when users of *LSD* act on the vivid and potent hallucinations they experience.
- Marijuana is one of the most commonly abused substances, and its psychoactive component *tetrahydrocannabinol* (*THC*) typically produces physical relaxation and a sense of novelty. Chronic users, particularly adolescents, can experience a decrease in short-term memory, and acute toxicity includes decreased motor coordination and impaired driving ability.
- *Ethanol* is the most commonly misused substance, and large doses result in CNS depression, while sudden cessation of chronic heavy use can result in profound CNS stimulation. Both acute and chronic effects of *ethanol* are common reasons for emergency department visits.
- Prescription drug misuse has necessitated efforts to restrict supply, and this led to an increase in use of *heroin*, *fentanyl,* and *fentanyl* analogs.

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STUDY QUESTIONS

Choose the ONE best answer.

47.1 A 15-year-old patient has been told that marijuana may help his anxiety. Which adverse effect has been associated with marijuana and may be a reason for this patient to avoid use of marijuana?

A. Short-term memory loss
B. Hyperthermia
C. Hepatitis
D. Hyponatremia

Correct answer = A. Short-term memory loss is observed with marijuana use and is more pronounced in adolescents. Hyperthermia, hepatitis, and hyponatremia have not been associated with marijuana use.

47.2 A 21-year-old college student is curious about the effects of LSD. She asks what type of risks may be involved with using the drug for the first time. Which of the following is a correct response to her question?

A. Exaggerated hallucinations
B. Cardiomyopathy
C. Hyperphagia
D. Bronchitis

Correct answer = A. Exaggerated hallucinations, sometimes known as “bad trips,” may occur, even in first-time users. These hallucinations can lead to extreme panic, which has caused individuals to react in a manner very uncharacteristic of their typical behavior.

47.3 A 58-year-old man is brought into the emergency department following an automobile accident. His blood alcohol level on admission is 280 mg/dL. He has been treated in the past for seizures related to alcohol use disorder, and he

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confirms that he has been drinking heavily over the past month since losing his job. What treatment should be given to this patient if he begins to go into alcohol withdrawal while hospitalized?

A. Acamprosate
B. Lorazepam
C. Naltrexone
D. Disulfiram

Correct answer = B. Should this patient go into alcohol withdrawal, he will likely also have seizures associated with it, given his past history. Benzodiazepines are used to treat seizures associated with alcohol withdrawal. These drugs stimulate the $GABA_A$ receptors, causing a decrease in neuronal activity and sedation. Acamprosate, naltrexone, and disulfiram may be considered at a later time to treat the alcohol dependence but would not be useful in the acute withdrawal setting.

47.4A 35-year-old man has been misusing cocaine and is agitated, tachycardic, hypertensive, and hyperthermic. Which of the following is the most appropriate initial treatment?

A. This patient should undergo gastric lavage (have his stomach pumped immediately).
B. Atropine should be administered to reverse the CNS depression that can occur with cocaine toxicity.
C. Benzodiazepines should be administered to calm the patient and decrease heart rate, blood pressure, and body temperature.
D. Phenobarbital should be the first choice as an anticonvulsant.

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Correct answer = C. Benzodiazepines such as lorazepam have anxiolytic properties and can calm a cocaine-toxic patient, thereby decreasing heart rate and blood pressure. As the patient becomes less agitated, movement will decrease and body temperature drops. In addition, the use of benzodiazepines decreases the chance of the patient experiencing a convulsion and would be the first choice to treat cocaine-induced convulsions.

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47.5 A 22-year-old man with a history of substance abuse arrives in the emergency department hypertensive, hyperthermic, and tachycardic. He also presents with altered mental status and hyperreflexia. Which substance is most likely causing these symptoms?

A. Ethanol
B. Bath salts
C. Heroin
D. Marijuana

Correct answer = B. “Bath salts” often contain synthetic cathinones. These products can cause an amphetamine-like sympathomimetic toxidrome, as well as serotonin syndrome, which would be treated with symptomatic/supportive care and possibly a serotonin antagonist such as cyproheptadine. In addition, synthetic cathinones are usually not detected on urine toxicology screening, so often evaluation of symptoms is used to determine the substance ingested. Ethanol, marijuana, and opioids would not produce these effects.

47.6 Which of the following agents contains the psychoactive alkaloid THC?

A. N-bomb
B. Khat
C. LSD
D. Marijuana

Correct answer = D. THC is the main psychoactive alkaloid contained in marijuana. N-bomb is a synthetic hallucinogen derived from mescaline. Khat is a shrub containing cathinones and does not contain THC. LSD is also a psychoactive drug but contains lysergic acid diethylamide.

47.7 Which drug has clinical effects similar to those of cocaine?

A. LSD
B. Marijuana

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C. Methamphetamine
D. Ethanol

Correct answer = C. Cocaine and methamphetamine have similar stimulant effects such as anxiety, tachycardia, hypertension, hyperthermia, and increased alertness. The stimulant effects can lead to arrhythmias, stroke, or myocardial infarction. LSD and marijuana cause primarily psychoactive effects such as hallucinations and paranoia. Ethanol is a depressant that produces the opposite effects of stimulants, including relaxation, drowsiness, and in high doses hypothermia.

47.8 Which drug leads to the formation of a cardiotoxic metabolite when administered with cocaine?

A. Lorazepam
B. Marijuana
C. Ethanol
D. Khat

Correct answer = C. Cocaine combined with ethanol forms cocaethylene, which may lead to aggressive and impulsive behaviors, as well as the potential for sudden myocardial infarction.

47.9 Which agent is often found as an adulterant in heroin and has led to an increase in deaths due to overdose?

A. LSD
B. Carfentanil
C. Marijuana
D. Cathinones

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Correct answer = B. Fentanyl and fentanyl derivatives, such as carfentanil, are often found in samples of heroin. Fentanyl derivatives are often many times more potent than heroin or fentanyl, which has led to a significant increase in overdose in recent years.

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47.1 Death secondary to MDMA use has occurred secondary to which adverse effect?

A. Respiratory depression
B. Acute kidney injury
C. CNS depression
D. Hyperthermia

Correct answer = D. MDMA (also known as ecstasy), is a stimulant with properties similar to those of cocaine. The stimulant effects may include hyperthermia, hypertension, and tachycardia.

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48

Pharmacogenomics

Emily J. Cicali, Kelsey Jean Cook

I. OVERVIEW

Genomic medicine describes how genes affect health. Precision medicine, also known as personalized medicine, is a broad area of medicine that focuses on tailoring care to the individual. Pharmacogenomics is a growing field within precision medicine that examines the impact of genetic variation on drug response. By better understanding factors that influence drug response, including genetics, drug therapy can be better customized to the individual.

II. PHARMACOGENOMICS

Present-day prescribing typically uses a “one size fits all” approach. Yet, the same drug and dose can lead to a wide range of responses in different patients (Figure 48.1). Pharmacogenomics attempts to better predict how an individual may respond to a drug based on their genetics. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has identified over 250 drugs with pharmacogenomic implications, with more than 40 medications rated as having the highest level of evidence (level A) for changing prescribing.

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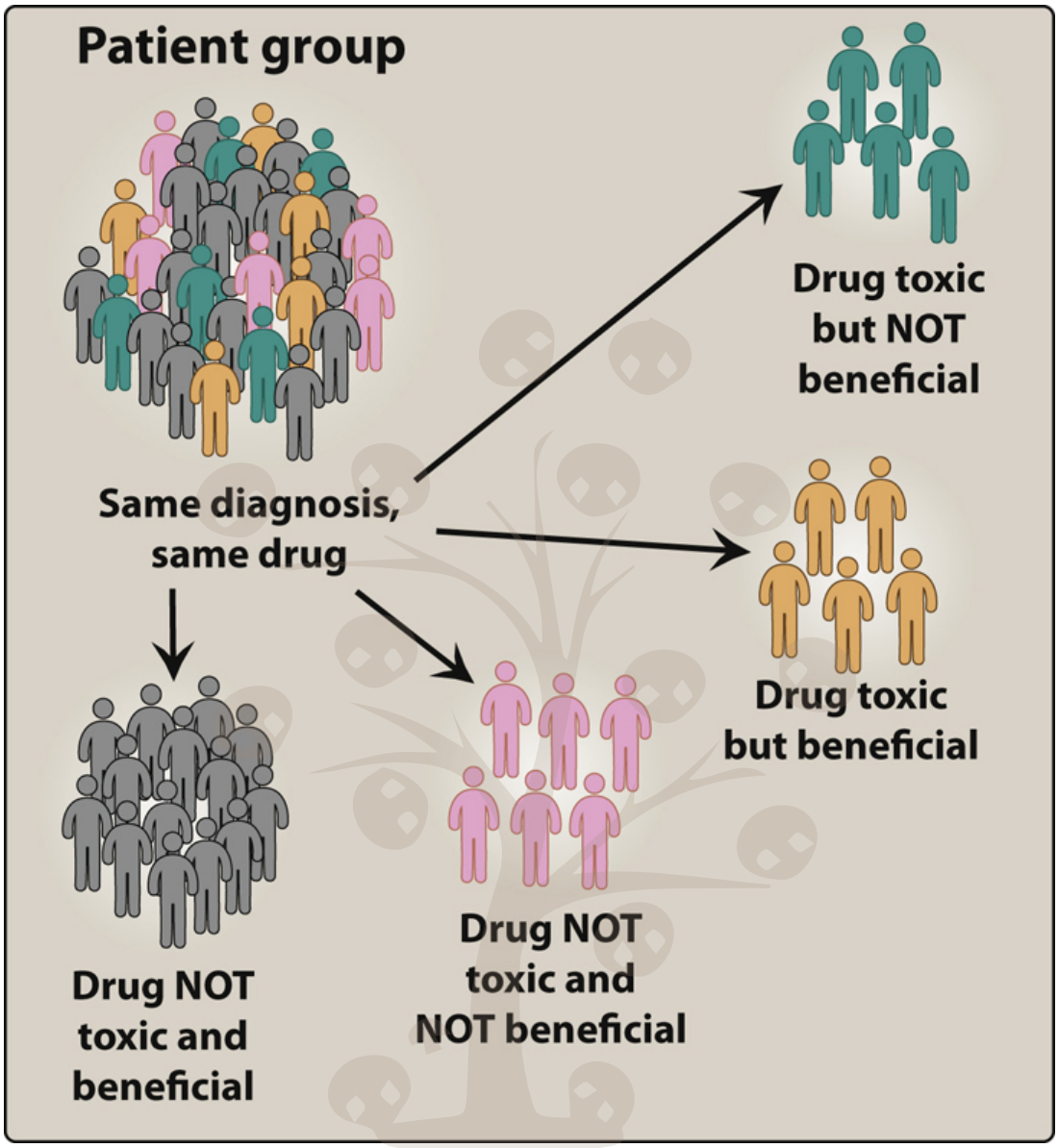

Figure 48.1 Pharmacogenomics definition.In a “one size fits all” approach, some individuals respond as expected, while others experience drug toxicity and/or ineffectiveness. Pharmacogenomics attempts to predict the response and mitigate unwanted effects by implementing dose adjustments or alternatives.Adapted from J. K.Hicks , H. L.McLeod . *Genomic and Precision Medicine*, 3rd ed. Elsevier (2017).

A. Definitions

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Alleles are variant forms of genes, such as B for brown or b for blue eye color traits (Figure 48.2). In pharmacogenomics, alleles are typically reported using star nomenclature (for example, *4) as a way to concisely report genetic variation. A particular star allele for a gene can represent a single nucleotide polymorphism (SNP) or a group of variations inherited as a haplotype. A lack of identified genetic variation defaults to a *1 designation. A genotype is an individual's collection of genes, such as BB, Bb, or bb for eye color. In pharmacogenomics, genotype is often used to refer to a single gene (for example, *1/*4). A phenotype is an observable trait, such as brown or blue eyes (Figure 48.2). Pharmacogenomics uses the genotype results to predict a phenotype. The translation from genotype to phenotype involves evaluation of the individual alleles of the genotype and the corresponding functional status. The functional status is assigned based on the level of protein activity associated with the allele: increased, normal, decreased, no, unknown, or uncertain function. The combination of alleles is used to predict the overall phenotype based on standardized translations (Figure 48.3). The phenotype classifications used in pharmacogenomics vary based on the type of protein. Phenotypes for drug-metabolizing enzymes describe the overall enzyme activity level as a metabolizer status that may be classified as poor, intermediate, normal, rapid, or ultrarapid (Figure 48.4). Phenotypes for drug transporters describe the level of protein function and are categorized as poor/low, intermediate, or normal function. In some cases, the phenotype is reported as positive or negative to reflect the presence or absence of the variant in question (for example, genes that are associated with hypersensitivity reactions).

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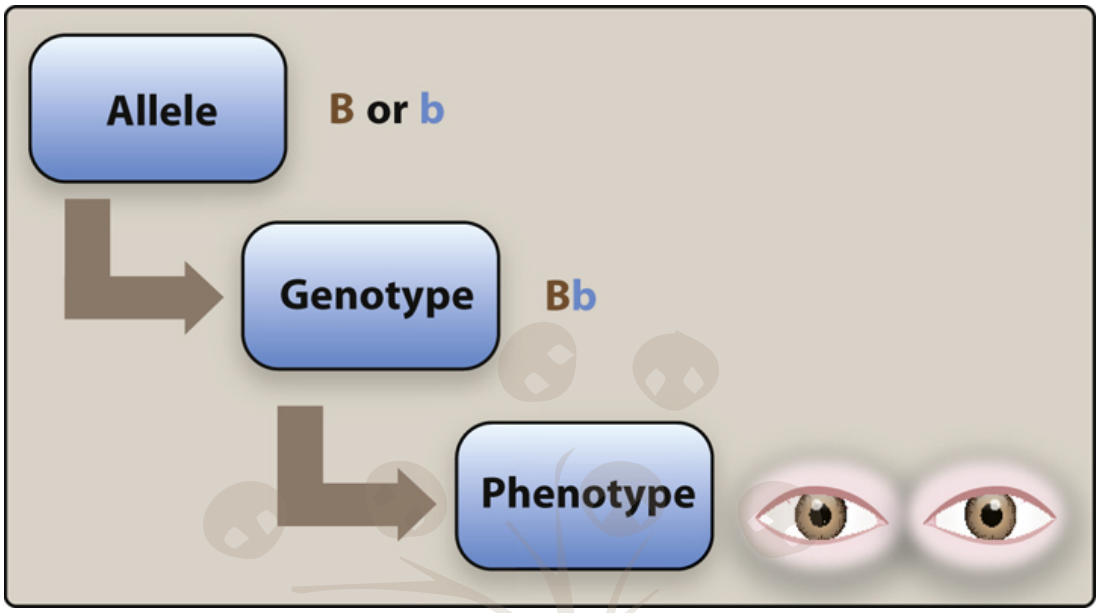

Figure 48.2 Genetic terminology.Each individual has two alleles, one from each parent, and the two alleles make up the genotype, which represents the gene. The phenotype is the outward expression, or observable trait, of the genotype.

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	Allele Functional Status and Phenotype Translations		
	PHENOTYPE	OVERALL ACTIVITY LEVEL	ALLELE COMBINATION(S)
Drug Metabolizing Enzyme Phenotypes	Poor metabolizer	Little to no enzyme activity	Combination of no function and/or decreased function alleles
	Intermediate metabolizer	Decreased enzyme activity (between normal and poor metabolizer)	Combinations of normal function, decreased function, and/or no function alleles
	Normal metabolizer	Fully functional enzyme activity	Combinations of normal function and decreased function alleles
	Rapid metabolizer	Increased enzyme activity (between normal and ultrarapid metabolizer)	Combinations of normal function and increased function alleles
	Ultrarapid metabolizer	Significantly increased enzyme activity (more thanrapid metabolizer)	Combination of two increased function alleles or more than two normal function alleles
Drug Transporter Phenotypes	Poor function	Little to no transporter function	Combinations of no function alleles and/or decreased function alleles
	Decreased function	Decreased transporter function (between normal and poor function)	Combinations of normal function, decreased function, and/or no function alleles
	Normal function	Fully functional transporter function	Combinations of normal function and/or decreased function alleles
	Increased function	Increased transporter function (compared to normal function)	One or more increased function alleles

Figure 48.3 Phenotype translations of drug-metabolizing enzymes and drug transporters.Adapted from K. E.Caudle , et al. *Genet Med*. 19(2): 215–223 (2017).

POLE STAR

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Figure 48.4 Drug-metabolizing enzyme phenotypes.The extent of enzyme activity results in varying drug levels in the body, as represented by the amount of color in each phenotype figure.

B. Pharmacogenomic resources

A variety of resources are available to provide information on the rapidly evolving field of pharmacogenomics. CPIC publishes peer-reviewed, evidence-based clinical guidelines for various gene-drug pairs. The guidelines provide graded recommendations for medication use in patients when pharmacogenetic testing data are available; however, the guidelines do not address who and when to test. CPIC also creates resources to help with clinical implementation of pharmacogenomics, such as clinical decision support algorithms. PharmGKB is a publicly available, interactive knowledge base that provides information about the impact of genetic variation on drug response. It contains various categories of information, including prescribing information, diagrams outlining pathways of drug metabolism (curated pathways), and drug label, clinical, and variant annotations. The Association for Molecular Pathology (AMP) Pharmacogenomics Working Group publishes recommendations on variations to include in pharmacogenomic testing panels. The AMP gene-specific guidelines categorize alleles for a specific gene as “must include” (Tier 1) or “optional” (Tier 2) for genotype testing based on factors such as allele function, population frequency, and availability of reference materials. The tiered system aims to promote standardization of testing across different laboratories. In addition to pharmacogenomic information included in some drug labels, the FDA has a “Table of Pharmacogenetic Associations” that categorizes gene-drug pairs into three sections: (1) pharmacogenetic associations for which data support therapeutic management recommendations; (2) pharmacogenetic associations for which data indicate a potential impact on safety or response; and (3) pharmacogenetic associations for which data

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demonstrate a potential impact on pharmacokinetic properties only.

III. DRUG-METABOLIZING ENZYMES

Drug-metabolizing enzymes (DMEs) are a diverse group of proteins that metabolize a wide variety of xenobiotic chemicals (for example, drugs, pollutants, endogenous chemicals). Their primary role is to transform compounds into more hydrophilic, polar entities to enhance elimination of xenobiotic chemicals from the body. This typically leads to pharmacologically inactive metabolites but sometimes leads to the formation of metabolites with pharmacologic activity, as is the case with prodrugs. DMEs can be affected by genetic polymorphisms in the genes that encode for their creation. This genetic variation can lead to differences in the level of enzyme activity, ranging from little to no activity (poor metabolizer) to increased activity (rapid or ultrarapid metabolizer). Differences in the activity of DMEs can significantly affect drug clearance or activation and, ultimately, efficacy and safety. The cytochrome P450 (CYP) family of enzymes is responsible for metabolism of most commonly used drugs. Therefore, most of the DMEs included in the CPIC guidelines are CYP450 enzymes. The overall impact of genetic variation in DMEs on drug response depends on the level of enzyme activity and the role of the DME in the breakdown or activation of a specific drug (Figure 48.5). Possible phenotypes for DMEs are poor metabolizer (PM), intermediate metabolizer (IM), normal metabolizer (NM), rapid metabolizer (RM), and ultrarapid metabolizer (UM).

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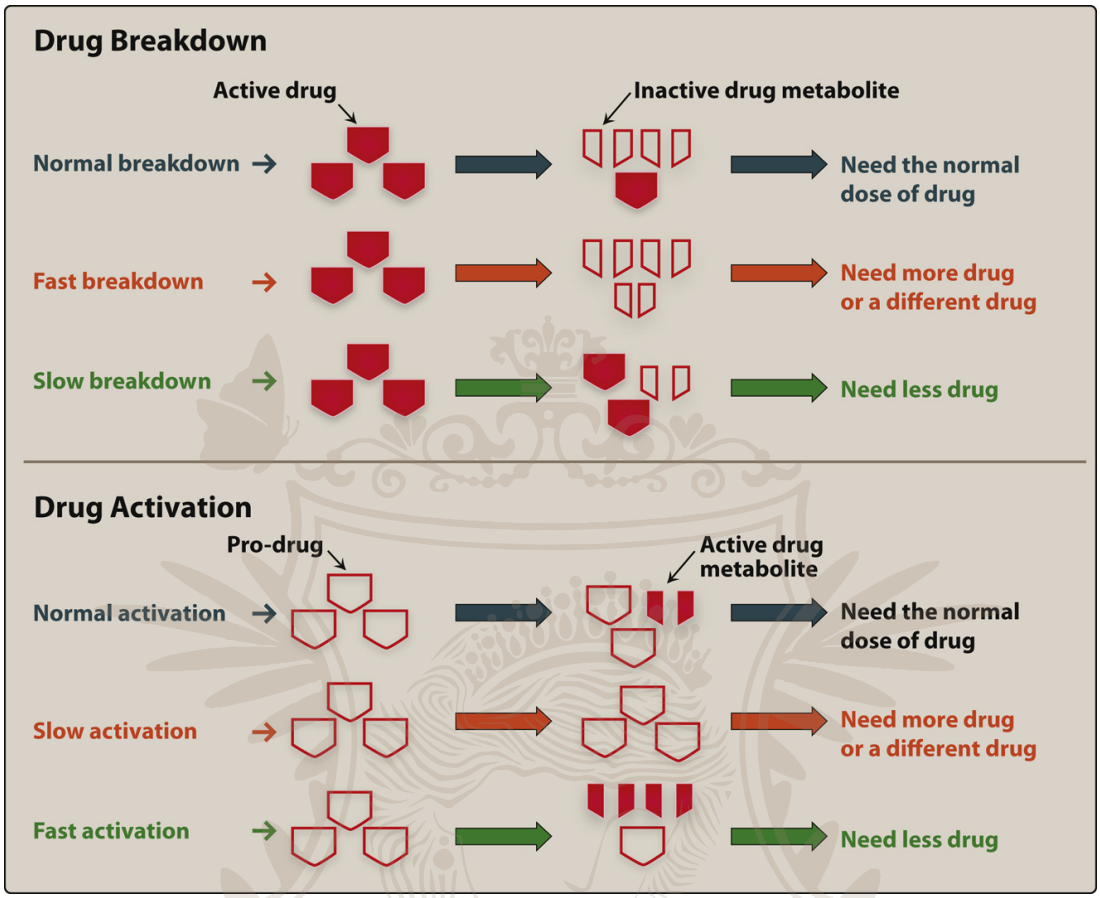

Figure 48.5 Impact of drug-metabolizing enzymes on drug response based on individual phenotype and the role of the enzyme in drug metabolism.Source: From the Centers for Disease Control and Prevention, Genomics and Precision Health Topics, Pharmacogenomics. Available at https://www.cdc.gov/genomics/disease/pharma.htm.

A. CYP2C19

The CYP2C19 enzyme metabolizes approximately 10% of drugs, including but not limited to *clopidogrel*, certain selective serotonin reuptake inhibitors, and proton pump inhibitors. Currently there are 38 identified CYP2C19 star alleles, three of which are classified as Tier 1 (“must test”) variants by the AMP. Tier 1 alleles for CYP2C19 include two no function alleles, *2 and *3, and one increased function allele, *17. If these variants are not identified, then it is presumed the individual has normal function allele(s), *1.

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Phenotypes for CYP2C19 are defined based on the specific combination of alleles in an individual, as described in Figure 48.3. CYP2C19 encompasses all five phenotype groups, and an example genotype for each phenotype group of CYP2C19 is found in Figure 48.6. The *2 allele frequency is higher in Asian populations (27%), as compared with European or African American populations (15% and 18%, respectively). As a result, Asian populations have an increased frequency of IMs and PMs. In contrast, the *17 allele is more frequent in Europeans (22%), which results in a higher frequency of RMs and UMs.

DRUG METABOLIZING ENZYME PHENOTYPES	EXAMPLE GENOTYPES		
	CYP2C19	CYP2D6	CYP2C9
Poor Metabolizer	*2/*2	*4/*4	*3/*3
Intermediate Metabolizer	*1/*3	*1/*4	*1/*2
Normal Metabolizer	*1/*1	*1/*1	*1/*1
Rapid Metabolizer	*1/*17	—	—
Ultrarapid Metabolizer	*17/*17	*1/*2x2	—

Figure 48.6 Example genotypes and phenotypes of drug-metabolizing enzymes.CYP = cytochrome P-450.

1.Clopidogrel: *Clopidogrel* is a thienopyridine prodrug that requires a two-step biotransformation to its active metabolite. The active metabolite is responsible for the antiplatelet effects of *clopidogrel*, mediated via antagonist effects at the $P2Y_{12}$ receptor on platelets. CYP2C19 is the primary DME involved in both steps, with several others contributing to a lesser extent. Individuals who are CYP2C19 IMs or PMs have reduced levels of the active metabolite of *clopidogrel* and higher on-treatment platelet aggregation as compared with NMs. A large body of evidence links CYP2C19 genotype with clinical outcomes among patients with acute coronary syndrome treated with *clopidogrel*, particularly those

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undergoing percutaneous coronary intervention. Specifically, individuals with reduced CYP2C19 enzyme activity (IMs and PMs) have an increased risk for major adverse cardiovascular events as compared with those with normal activity. As such, the CPIC guidelines recommend an alternative antiplatelet agent in these patients, such as *prasugrel* or *ticagrelor,* if no contraindications to the alternatives exist. This recommendation is classified as strong for PMs and moderate for IMs. Additionally, the product labeling includes a boxed warning that CYP2C19 PMs are at higher risk for cardiovascular events and alternative treatment should be considered. Individuals who carry the *17 allele (RMs and UMs) have increased CYP2C19 activity, and some studies have reported enhanced platelet inhibition and potentially increased risk of bleeding. However, emerging evidence has shown that the risk of bleeding for RMs or UMs on *clopidogrel* is lower than that with more potent $P2Y_{12}$ receptor antagonists (*prasugrel*, *ticagrelor*). Therefore, CPIC recommends using *clopidogrel* at standard doses (strong recommendation) for CYP2C19 RMs and UMs.

Clinical Application 48.1: Choice of Antiplatelet Therapy Based on Genetic Results

A 62-year-old man was discharged from the hospital 3 weeks ago following an ST-segment elevation myocardial infarction treated with percutaneous coronary intervention. He presents today to an outpatient cardiologist for follow-up. His past medical history includes stroke, diabetes, and hypertension. Current medications include *ticagrelor*, *aspirin*, *lisinopril*, *metoprolol,* and *metformin.* The cardiologist is assessing appropriateness to de-escalate antiplatelet therapy from *ticagrelor* to *clopidogrel.* CYP2C19 genetic results are available and genotype is *2/*17. This genotype combination is one no function allele (*2) and one increased function allele (*17). Evidence shows that the *17 does not overcome the lack of activity provided from *2, and this genotype is classified as an IM. As such, *clopidogrel* should be avoided in this individual if alternatives can be given without contraindications. *Prasugrel* is not appropriate due to the history of stroke, but *ticagrelor* is appropriate to continue. Therefore, therapy should not be de-escalated at this time.

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2.Selective serotonin reuptake inhibitors: *Citalopram, escitalopram,* and *sertraline* are selective serotonin reuptake inhibitors (SSRIs) that are metabolized by CYP2C19 (Figure 48.7). They are administered as pharmacologically active drugs and then undergo metabolism to less active or inactive metabolites by several DMEs, with CYP2C19 contributing the most. *Citalopram* is a racemic mixture of R- and S-enantiomers. The S-enantiomer is pharmacologically active and is marketed as *escitalopram.* SSRIs are used to treat depression and anxiety disorders (see Chapters 16 and 17). Variations in CYP2C19 may put individuals at risk for poor therapeutic outcomes, as the pharmacokinetics of these SSRIs are directly impacted by genotype. If genotype is utilized, the risk of poor outcomes may be reduced.

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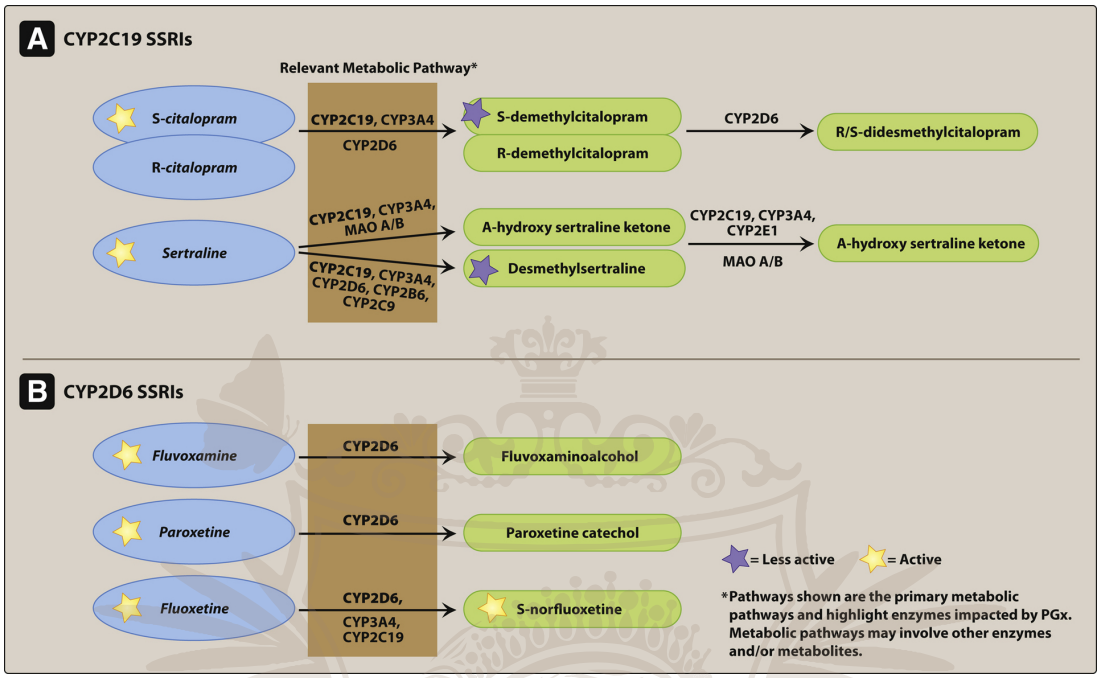

Figure 48.7 Selective serotonin reuptake inhibitors are metabolized primarily (bolded enzyme) by either CYP2C19 (panel **A**) or CYP2D6 (panel **B**) from an active parent drug to a less active or inactive metabolite.MAO = monoamine oxidase; PGx = pharmacogenomics.

CYP2C19 UMs have significantly lower drug concentrations of *citalopram* and *escitalopram*, as compared with NMs. The increased activity of CYP2C19 results in less active drug, putting the individual at risk for pharmacotherapy failure. CPIC guidelines recommend an alternative SSRI not metabolized by CYP2C19 for RMs and UMs. Decreased enzyme activity, as seen with IMs and PMs, results in slightly and highly elevated concentrations of active drug for these SSRIs, respectively. The higher active drug concentrations in PMs may increase the risk of adverse effects, and CPIC guidelines recommend considering an alternative SSRI. In addition, CPIC guidelines also recommend that, if *citalopram*/*escitalopram* use is warranted, the starting dose should be decreased by 50% in PMs. The product labeling for *citalopram* has a maximum recommended dose of 20 mg in CYP2C19 PMs to avoid the risk of QTc prolongation.

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Sertraline, while also primarily metabolized by CYP2C19, has only been shown to have a slightly increased metabolism from the parent drug to metabolites in CYP2C19 UMs, but data support decreased metabolism in PMs. Similar to the other CYP2C19-mediated SSRIs, a 50% reduction in the starting dose is recommended for PMs in the CPIC guidelines. Alternatively, PMs should be prescribed a different SSRI not metabolized by CYP2C19.

B. CYP2D6

The CYP2D6 enzyme is responsible for metabolism of numerous drugs, including certain SSRIs and opioids. CYP2D6 is a highly polymorphic gene with over 130 identified core variants, ranging from no function alleles to normal function alleles. The CYP2D6 gene is also subject to copy number variation (deletions and duplications). Copy number variation in genes is denoted by "xN," where N represents the number of CYP2D6 gene copies in cis. Due to the complex nature of the CYP2D6 gene, and in an effort to standardize phenotype translations and clinical recommendations, a CYP2D6 activity scoring system is used to translate genotype to phenotype. The individual alleles are each assigned an activity value of 0, 0.25, 0.5, or 1 for no, very decreased, decreased, or normal function, respectively. The values for each of the alleles in the genotype are added to get the total activity score. For alleles with multiple copies, the individual allele value is multiplied by the number of copies present. Finally, the activity score is used to translate the genotype to phenotype (Figure 48.8). For example, CYP2D6*1 × 2/*4 is assigned an activity score of 2. The CYP2D6 *1 allele is a normal function allele and gets an activity value of 1, but there are 2 copies, so it is assigned an activity value of 2 (1 × 2 = 2). The CYP2D6*4 allele is a no function allele and gets an activity value of 0. The two values are then added together, 2 + 0, to get an overall activity score of 2, which translates to CYP2D6 NM. Of note, PMs are most frequent in European populations (approximately 6%) and

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are less frequent in Latino and African American populations (3% and 2%, respectively).

CYP2D6 ACTIVITY SCORE	CYP2D6 PHENOTYPE
0	Poor metabolizer
0<X<1.25	Intermediate metabolizer
1.25≤X≤2.25	Normal metabolizer
>2.25	Ultrarapid metabolizer

Figure 48.8 Relationship of CYP2D6 activity score to phenotype translation.Adapted from J. K.Hicks, J. R.Bishop, K.Sangkuhl, et al. Supplement to: Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of SSRIs. Available at https://files.cpicpgx.org/data/guideline/publication/SSRI/2015/25974703-supplement.pdf.

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CYP2D6 is also subject to phenoconversion, a phenomenon whereby an external nongenetic factor, such as a drug interaction or comorbidity, alters the predicted phenotype (Figure 48.9). Phenoconversion has been most extensively studied for CYP2D6, with a large focus on drug interactions. Drug interactions are incorporated when calculating an activity score to determine the

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predicted clinical phenotype. Once the activity score is calculated, if a patient is also taking a CYP2D6 inhibitor, the activity score is multiplied by 0 for use of a strong inhibitor or 0.5 for use of a moderate inhibitor. Using the previous example (CYP2D6*1 × 2/*4 with an activity score 2), if the patient were also taking a strong CYP2D6 inhibitor, such as *bupropion* or *fluoxetine*, the activity score would be multiplied by 0, resulting in a final activity score of 0 (translating to a PM; Figure 48.8). For phenoconversion to occur, there must be a change in the predicted phenotype after accounting for the drug interaction (for example, NM converted to PM due to the use of a strong CYP2D6 inhibitor). Not all instances of initiation of a CYP2D6 inhibitor cause phenoconversion; this phenomenon depends on the initial activity score and effect of the CYP2D6 inhibitor. For example, a poor metabolizer cannot experience phenoconversion, as there is no baseline enzyme activity to alter, and 0 multiplied by any number results in 0 (PM).

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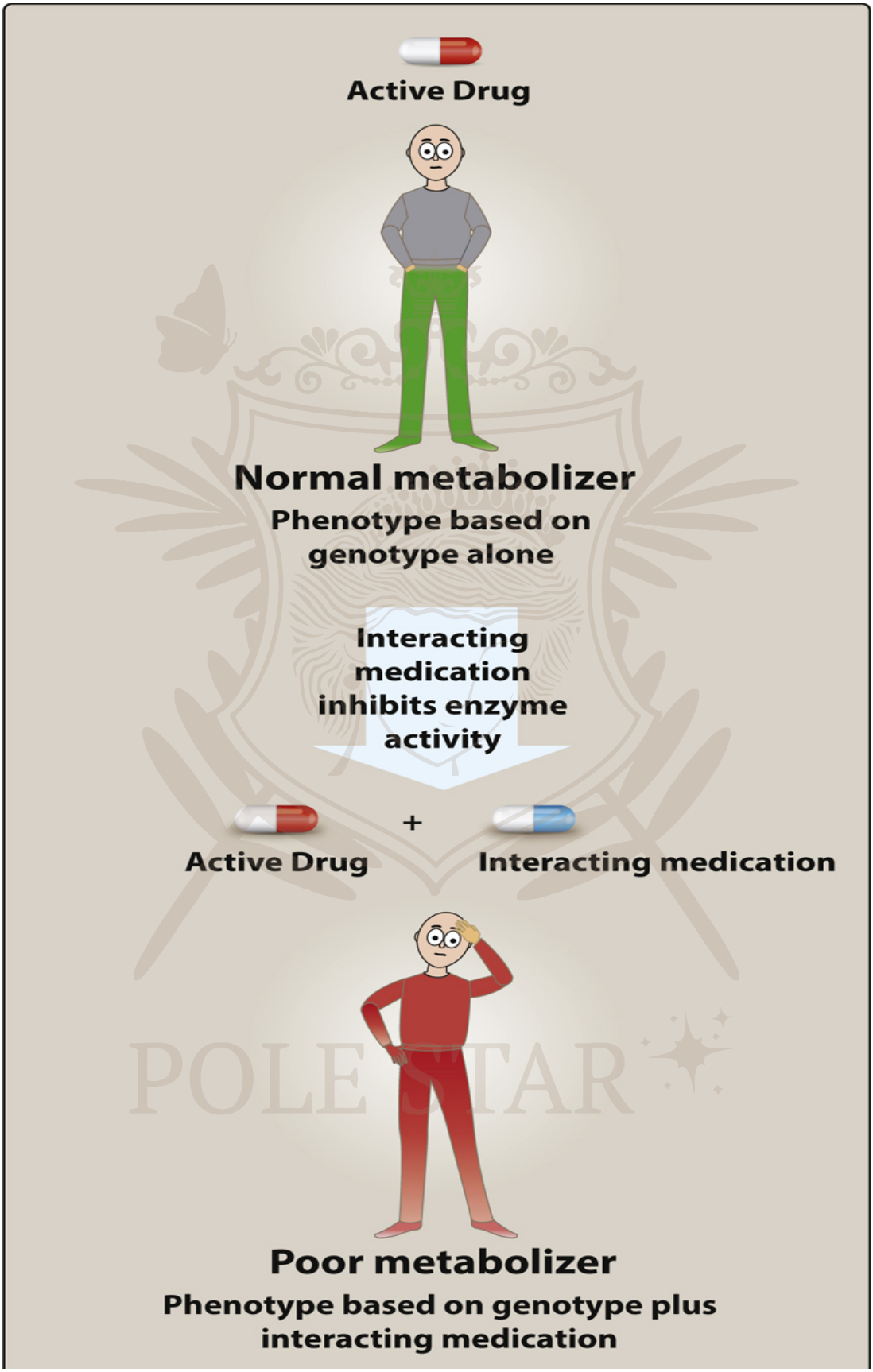
Active Drug
Normal metabolizer
Phenotype based on genotype alone
Interacting medication inhibits enzyme activity
+
Active Drug
Interacting medication
Poor metabolizer
Phenotype based on genotype plus interacting medication

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Figure 48.9 An individual's phenotype may differ from the predicted phenotype based on genotype in the presence of an interacting medication (for example, CYP2D6 inhibitor), a process referred to as phenoconversion.

1.Selective serotonin reuptake inhibitors: *Fluvoxamine* and *paroxetine* are two SSRIs that are primarily metabolized via CYP2D6 (Figure 48.7). They are pharmacologically active drugs that are converted to metabolites with little activity toward serotonin reuptake inhibition. Variations in CYP2D6 activity can lead to differences in patient exposure to the active drug, resulting in differences in drug response. CYP2D6 genotyping may help avoid an undesired response with these agents, especially when used in conjunction with CYP2C19 genotyping. CYP2D6 PMs have significantly decreased metabolism of *paroxetine* and *fluvoxamine* to less-active compounds, as compared with NMs. The resulting increase in plasma concentrations of active drug may increase the probability of adverse effects. CPIC guidelines recommend selecting an alternative drug not predominantly metabolized by CYP2D6 for CYP2D6 PMs. However, if *fluvoxamine* or *paroxetine* use is warranted, prescribers may consider a 25% to 50% or 50% reduction in the recommended starting dose, respectively (optional recommendation). For CYP2D6 IMs, it may be reasonable to monitor these patients more closely or consider a slower titration schedule. CYP2D6 UMs convert active *paroxetine* to less-active compounds more extensively than NMs, and lower or undetectable plasma concentrations may increase the probability of pharmacotherapy failure. CPIC guidelines recommend against the use of *paroxetine* for CYP2D6 UMs (strong recommendation). *Fluoxetine* is a strong inhibitor of CYP2D6, and it is also primarily metabolized to its active metabolite S-norfluoxetine via CYP2D6. Since the parent drug

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is active, and the total sum of the concentrations of *fluoxetine* and S-norfluoxetine are not impacted by CYP2D6 variation, there are no recommendations for dosage adjustments of fluoxetine in CYP2D6 polymorphisms.

2.Opioids: CYP2D6 plays a critical role in the metabolism of certain opioid analgesics. *Codeine*, *tramadol*, *hydrocodone*, and *oxycodone* are opioids that are converted to more active metabolites via CYP2D6. The role that the active metabolite plays depends on the relative efficacy and potency of the metabolite compared with the parent drug. For example, *codeine* and *tramadol* are heavily dependent on CYP2D6-mediated activation to *morphine* and O-desmethyltramadol, respectively (Figure 48.10), which are much more potent than their respective parent compounds and responsible for the primary analgesic effects of *codeine* and *tramadol.* CYP2D6 UMs have significantly higher concentrations of *morphine* or O-desmethyltramadol following administration of standard doses of *codeine* or *tramadol*, respectively, leading to a potential increased risk of toxicity, including life-threatening respiratory depression with standard dosing. CPIC guidelines recommend against *codeine* or *tramadol* use in CYP2D6 UMs (activity score >2.25; strong recommendation). CYP2D6-mediated metabolism of *codeine* and *tramadol* to more active compounds is significantly reduced in CYP2D6 PMs, leading to lower mean levels of *morphine* and O-desmethyltramadol, respectively. CYP2D6 PMs have also been shown to have reduced efficacy of both *codeine* and *tramadol*, as compared with NMs. CPIC guidelines recommend avoiding *codeine* or *tramadol* use in CYP2D6 PMs (activity score = 0; strong recommendation).

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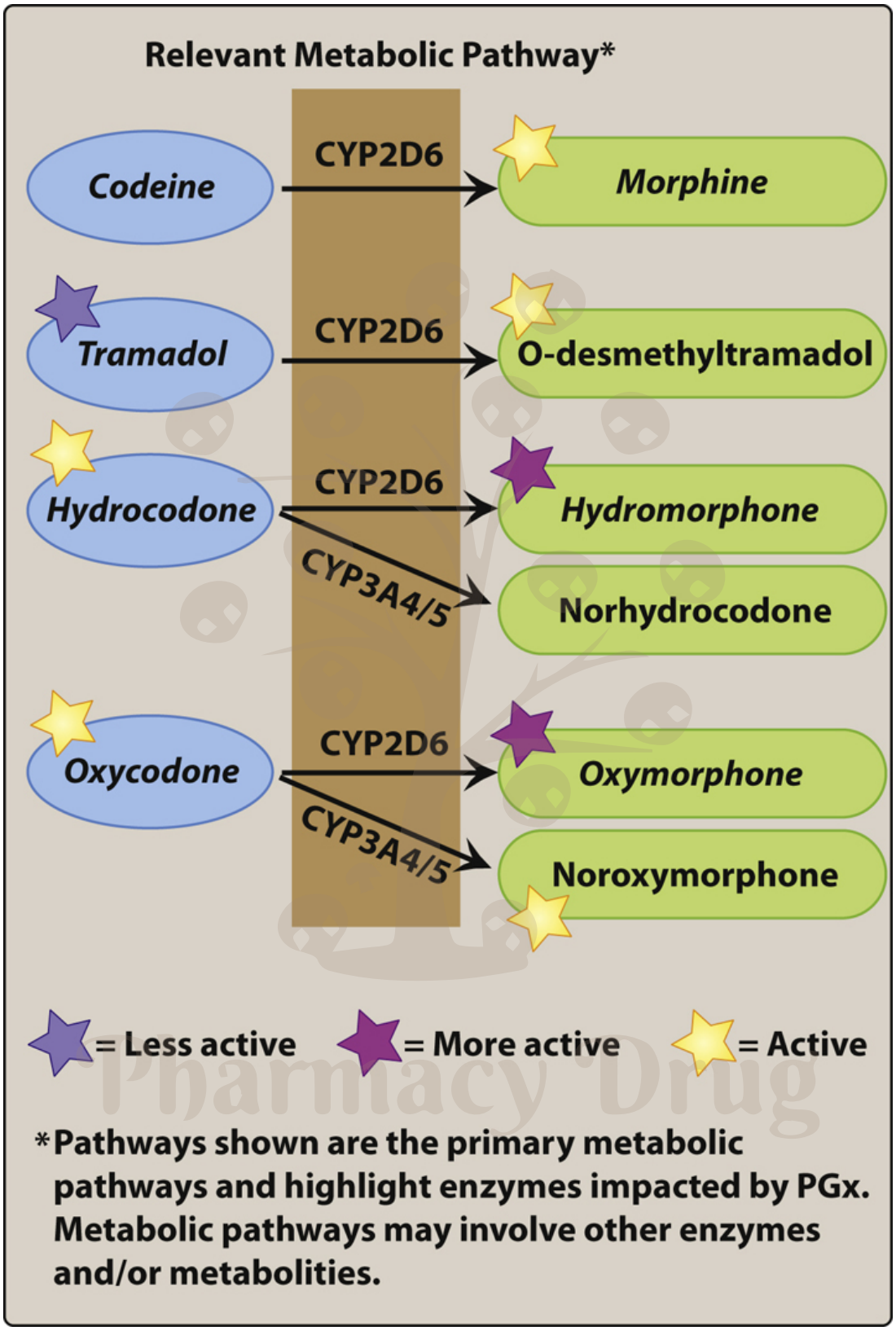

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Figure 48.10 Certain opioids (*codeine*, *tramadol*, *hydrocodone*, and *oxycodone*) are metabolized by CYP2D6 to more active metabolites that may be primarily responsible for analgesic effects.PGx = pharmacogenomics.

Hydrocodone and *oxycodone* are also converted via CYP2D6 to more potent active metabolites, *hydromorphone* and *oxymorphone*, respectively (Figure 48.10). The clinical response to these two opioids is not as dependent on CYP2D6 activation, as compared with *codeine* and *tramadol*, partly because the *hydrocodone* and *oxycodone* parent drugs have analgesic properties themselves. Only a small percentage of *hydrocodone* is metabolized via CYP2D6 to the minor metabolite *hydromorphone*, and the relationship between plasma *hydromorphone* or *hydrocodone* concentration and analgesic effect is unclear. CPIC recommends standard label age- or weight-specific dosing for CYP2D6 PMs and IMs (optional recommendation). If adequate pain control is not achieved, then an alternative opioid should be considered. *Oxycodone* is metabolized via CYP2D6 to the minor metabolite *oxymorphone.* The data for CYP2D6 variation and *oxycodone* are limited and conflicting; therefore, the CPIC has no recommendation for CYP2D6 metabolizer status and *oxycodone* use.

Clinical Application 48.2: Selection of Opioid Therapy Based on Genetic Results

A 57-year-old man is undergoing a right total knee arthroplasty and presents today for his preoperative appointment. He has a past medical history of hypertension, obesity, and depression. Current medications include *lisinopril*, *fluoxetine*, and *naproxen.* The surgeon is preparing him for his postoperative care, including a prescription for *tramadol* as needed for pain. CYP2D6 genetic results are available, and the genotype is *1/*4. This genotype combination is one normal function allele (*1, activity score = 1) and one no function allele (*4, activity score = 0). Based on genotype alone, the CYP2D6 activity score is 1 and translates to an IM. However, the patient is also taking *fluoxetine*, which is a strong CYP2D6 inhibitor. After accounting for the CYP2D6 inhibitor (multiply

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activity score by 0), the clinical phenotype is PM (activity score = 0). *Tramadol* is not an appropriate opioid analgesic for this patient, as CYP2D6 PMs have decreased efficacy with this agent due to decreased formation of O-desmethyltramadol, the active metabolite of *tramadol.* CPIC guidelines recommend an alternative opioid not heavily dependent on CYP2D6-mediated activation. Alternative opioid options include, but are not limited to, *morphine* or *hydromorphone. Oxycodone* may also be considered, but theoretically could have the same issue of ineffectiveness; however, data supporting this are limited.

C. CYP2C9

The CYP2C9 enzyme metabolizes approximately 15% of drugs, including *warfarin* and nonsteroidal anti-inflammatory drugs (NSAIDs). There are 70 identified star alleles, six of which are defined as Tier 1 (must test) variants by the AMP. Four of these alleles are classified as decreased function (*2, *5, *8, and *11), and the other two are classified as no function (*3 and *6). CYP2C9 is another gene that assigns activity values to star alleles to help with genotype to phenotype translation. Decreased function alleles have an activity value of 0.5, while no function alleles have an activity value of 0. The definitions in Figure 48.3 apply, but only three phenotype groups are relevant for CYP2C9. NMs have a CYP2C9 activity score of 2, IMs can either be 1.5 or 1.0, and PMs are either 0.5 or 0, which indicates that a CYP2C9 PM may have some enzymatic activity, but is greatly reduced as compared with IMs and NMs. Clinically relevant differences in allele frequencies exist between African Americans and Europeans. Specifically, *5, *6, *8, and *11 are very rare in Europeans (~0%-0.2%) but are detected in 1% to 6% of African Americans. The *2 and *3 alleles are frequent among Europeans, at 13% and 8%, respectively, but less frequent in African Americans at 2%. These frequencies result in IMs and PMs being more common in Europeans (35% and 3%, respectively), as compared with African Americans (24% and 0.5%, respectively).

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1.Warfarin: *Warfarin* is an oral anticoagulant that has a narrow therapeutic index and large interpatient variability in regards to the dosage required to remain in the therapeutic window (see Chapter 13). Many factors influence *warfarin* dosing requirements, including genetic variations in CYP2C9, VKORC1, and CYP4F2. *Warfarin* is administered as a pharmacologically active racemic mixture, with the S-enantiomer being more potent than the R-enantiomer in its ability to inhibit the drug target, vitamin K epoxide reductase complex subunit 1 (VKORC1). When VKORC1 is inhibited, it is not able to reduce vitamin K, which leads to decreased formation of clotting factors. CYP2C9 metabolizes S-*warfarin* into inactive metabolites (Figure 48.11). If variation resulting in decreased CYP2C9 enzyme activity is present, more active drug is available to exert the pharmacologic effect, resulting in a lower dose requirement to achieve the target INR. The drug target VKORC1 is also encoded by a gene with one well-studied variant, −1639 G>A. The A allele is associated with lower VKORC1 expression compared with the G allele, resulting in an individual being more sensitive to *warfarin* and requiring lower doses. CYP4F2 metabolizes reduced vitamin K, which removes it from the cycle. CYP4F2 variation is associated with reduced enzyme activity, which results in more vitamin K to form clotting factors, and, therefore, higher dose requirements to achieve the target INR.

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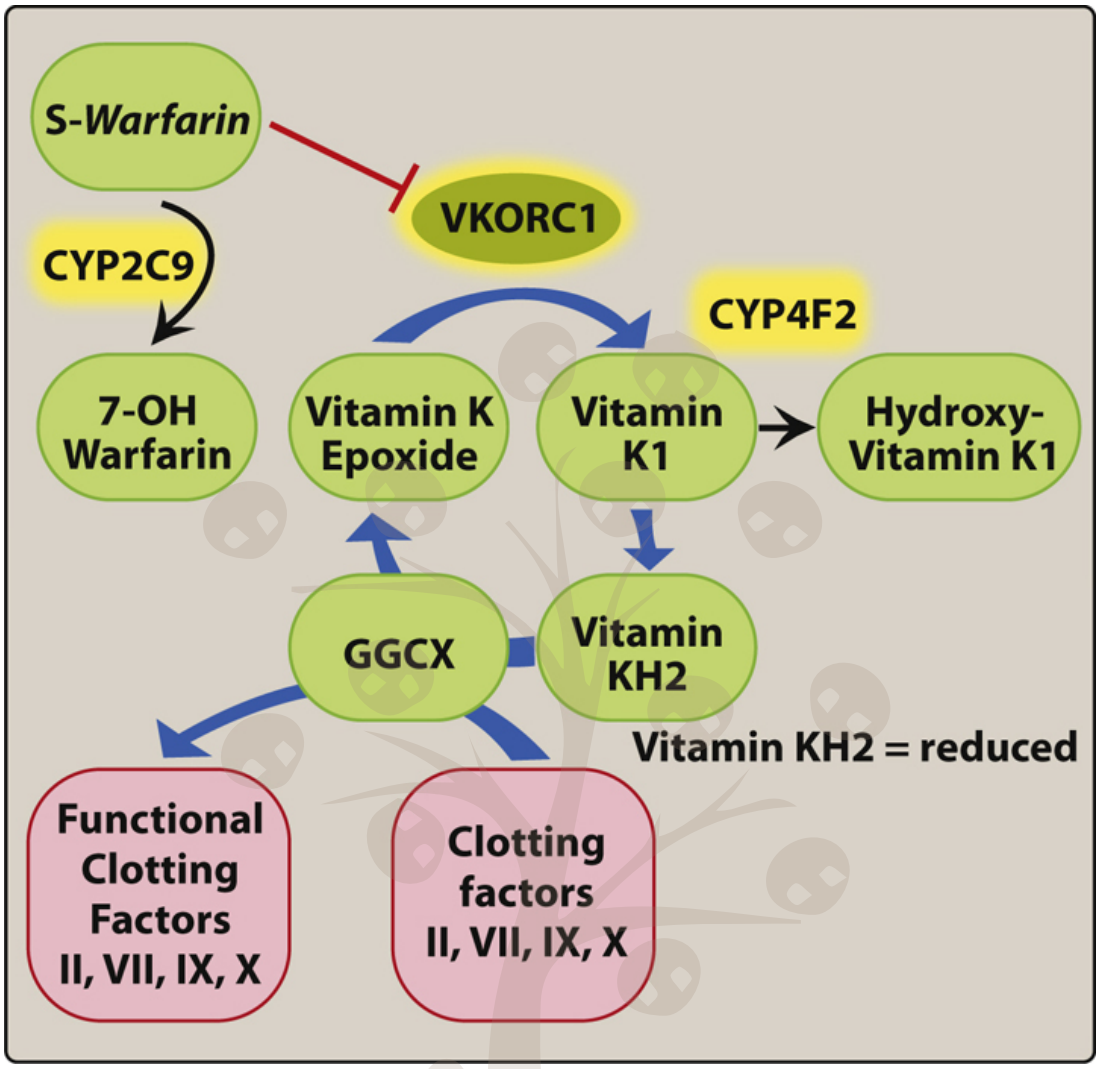

Figure 48.11 *Warfarin* is metabolized by CYP2C9 to an inactive metabolite.The drug target of *warfarin* is VKORC1, which has a function of reducing vitamin K to form clotting factors. CYP4F2 metabolizes reduced vitamin K, removing it from the cycle. GGCX = gamma-glutamyl carboxylase.

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The product labeling for *warfarin* includes a chart that shows three ranges of expected maintenance doses of *warfarin,* based on different combinations of genotypes for CYP2C9 and VKORC1. It is recommended to consider these ranges if genotype is known when choosing the initial *warfarin* dose. In addition to CYP2C9 IMs or PMs requiring lower doses, it may

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also take longer for these individuals to achieve a maximum effect for a given dose. It is important to point out that this chart only includes CYP2C9 *2 and *3 alleles, which as noted above are common variations in individuals with European ancestry. Overall, variations in CYP2C9, VKORC1, and CYP4F2 account for a large portion of *warfarin* dose variance but explain less of the variability for other ancestries. The CPIC *warfarin* guideline includes a dosing algorithm for genotype-based recommendations, rather than recommendations based on phenotypes. It is recommended to use a validated published pharmacogenetic algorithm (for example, warfarindosing.org) in certain scenarios. It is also recommended to increase the dose by 5% to 10% if the individual carries a CYP4F2 variant. Validated pharmacogenetic algorithms used for dosing *warfarin* include genetic variables along with clinical variables (for example, age, sex, weight, smoking status, interacting drugs) to allow for the best prediction of a *warfarin* maintenance dose.

2.Nonsteroidal anti-inflammatory drugs: NSAIDs (for example, *celecoxib, diclofenac, ibuprofen, meloxicam, naproxen)* are commonly used to treat mild-to-moderate pain (see Chapter 40). NSAIDs, such as *ibuprofen*, are administered as pharmacologically active agents and are primarily metabolized by CYP2C9, along with other DMEs, to inactive metabolites (Figure 48.12). Reduced activity of the CYP2C9 enzyme (IMs and PMs) has been associated with higher exposure to NSAID concentrations. While NSAIDs are generally considered safe, they have the potential to cause serious complications such as gastrointestinal bleeding, hypertension, myocardial infarction, and renal damage. Limited clinical evidence links a genetic variation in CYP2C9 to NSAID-associated adverse effects; however, as most NSAID adverse effects are dose dependent, it is reasonable to assume elevated concentrations increase the risk for adverse effects.

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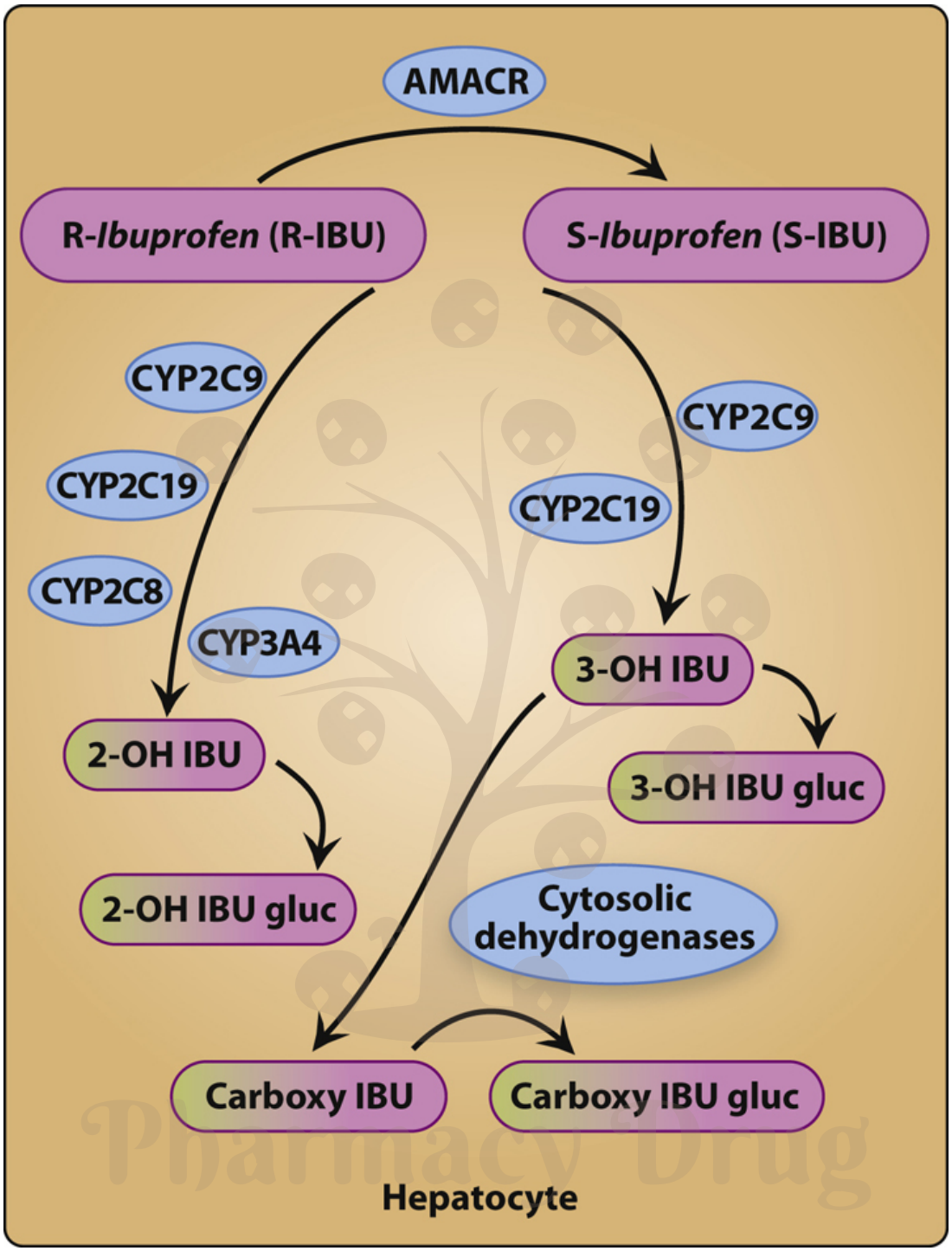

Figure 48.12 NSAIDs are metabolized primarily by CYP2C9 into several inactive metabolites.

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Celecoxib, *flurbiprofen, and ibuprofen* have short or moderately long half-lives (2-16 hours). CPIC guidelines recommend initiating these drugs with 25% to 50% of the lowest recommended starting dose in CYP2C9 PMs, and the lowest recommended starting dose in CYP2C9 IMs with an activity score of 1. *Meloxicam* has a longer half-life (15-20 hours), and that of *piroxicam* is even longer (30-86 hours). For both drugs, CPIC guidelines recommend an alternative not metabolized by CYP2C9 in PMs. This is also the same recommendation for IMs with an activity score of 1.0 for *piroxicam,* while for *meloxicam* it is recommended to initiate 50% of the lowest starting dose. For all NSAIDs, CPIC guidelines recommend initiation of the usual starting dose in NMs and IMs with an activity score of 1.5. The FDA Table of Pharmacogenetic Associations supports these recommendations in PMs for *celecoxib, flurbiprofen,* and *piroxicam,* where a dose reduction by 50% is recommended for *celecoxib* and a reduced dose is recommended for *flurbiprofen* and *piroxicam.*

IV. DRUG TRANSPORTERS

Transporters are membrane-bound proteins that move drugs, along with other endogenous and exogenous substances (for example, nutrients, cellular waste, toxins) across biologic membranes. Transporters are located throughout the body. The most important locations for drug transporters include the liver, kidney, intestine, and blood–brain barrier. Transporters promote either influx or efflux of drug molecules, which means they either move drug into or out of the cell, respectively (Figure 48.13). Genetic factors can impact transporter expression, which, in turn, can impact the efficacy or toxicity of a drug. For example, if an influx transporter has genetic variation resulting in decreased expression of the transporter, the drug will exhibit decreased entry into the cell and will accumulate in the extracellular space. This can cause toxicity, depending on the drug and location (for example, *simvastatin*-SLCO1B1 as described

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below). If an efflux transporter has genetic variation and a reduced expression of transporter, drug will not be pumped out of the cell and may accumulate intracellularly. This may also be problematic, although the exact response depends on the location and drug. Most drug transporters can be classified into one of two families: solute carrier or ATP-binding cassette.

Pharmacy Drug

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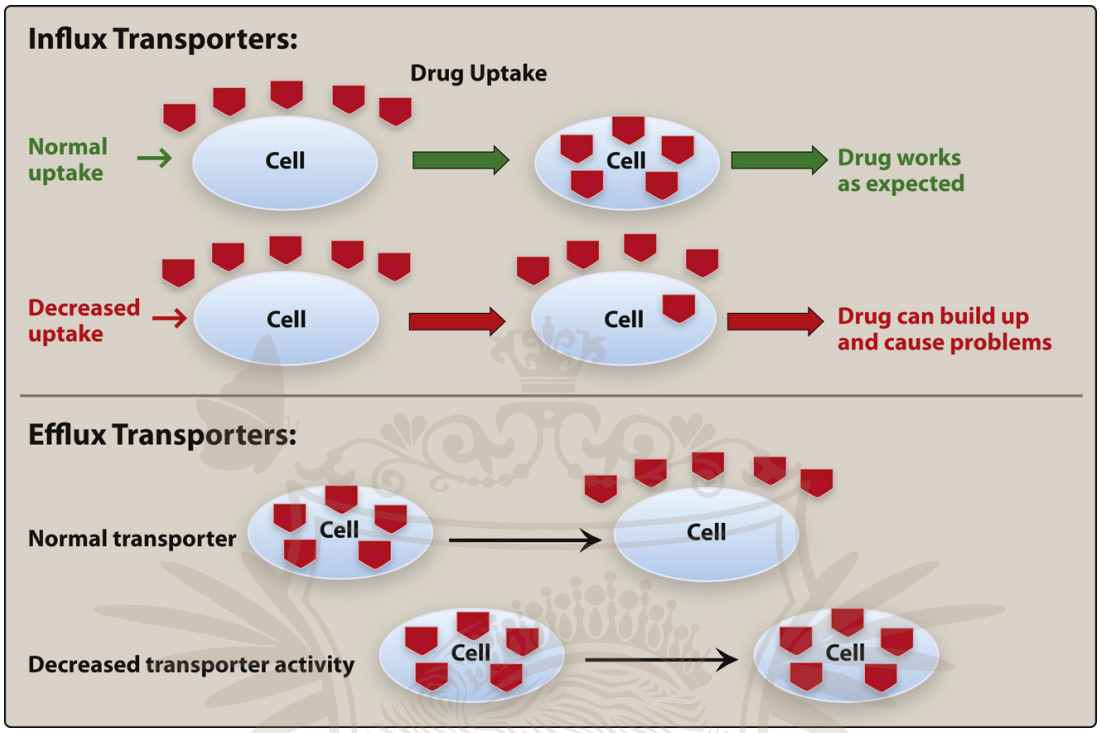

Figure 48.13 Transporters are membrane bound and move drugs either into (influx) or out of (efflux) of the cell.Genetic variation can result in reduced transporter expression, which results in less drug being moved across the membrane; the effect of this depends on the drug and transporter location.Adapted from M.Whirl-Carrillo , R.Huddart , L.Gong , K.Sangkuhl , C. F.Thorn , R.Whaley , and T. E.Klein . An evidence-based framework for evaluating pharmacogenomics knowledge for personalized medicine. *Clin. Pharmacol. Ther*. 110(3): 563–572 (2021) and M.Whirl-Carrillo , E. M.McDonagh , J. M.Hebert , L.Gong , K.Sangkuhl , C. F.Thorn , R. B.Altman , and T. E.Klein . Pharmacogenomics knowledge for personalized medicine. *Clin. Pharmacol. Ther*. 92(4): 414–417 (2012).

A. ATP-binding cassette transporters

These proteins bind adenosine triphosphate (ATP) and use the energy to drive the transport of molecules across the membrane. ATP-binding cassette (ABC) transporters are categorized into seven subfamilies from ABCA to ABCG, and there are a total of 48 known human ABC transporters. The most widely studied transporter is within the ABCB subfamily, referred to as ABCB1,

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P-glycoprotein, or multidrug-resistant (MDR) protein 1. P-glycoprotein (PGP), encoded by the gene ABCB1, is an efflux transporter responsible for preventing a wide variety of drugs and endogenous compounds from entering tissue locations where it is expressed (for example, liver, blood–brain barrier). PGP has multiple substrates, including but not limited to *cyclosporine, digoxin, fexofenadine,* and *ketoconazole.* In addition, several drugs inhibit or induce PGP (for example, *verapamil* or *carbamazepine*, respectively), contributing to drug–drug interactions. PGP genetic variation that results in decreased expression would be expected to lead to increased plasma concentrations when expressed in the intestine, liver, and kidney. This has been confirmed in some studies but has not been replicated. As such, there are no clinical recommendations for PGP genetic variations at this time.

B. Solute carrier transporters

There are approximately 350 known solute carrier (SLC) transporters in the human body. Unlike ABC transporters, SLC transporters do not require ATP to transport molecules across the membrane. The most common SLC transporters are Organic Anion Transporter Polypeptides (OATPs), Organic Cation Transporters (OCTs), and Organic Anion Transporters (OATs), among many others. OATPs are some of the most studied. They consist of a family of 11 influx transporters expressed in many tissues (for example, liver, kidney) and facilitate drug uptake.

1. **OATP1B1:** The SLCO1B1 gene is responsible for encoding the OATP1B1 transporter, a hepatic transporter on the sinusoidal membrane, which is responsible for moving drugs (for example, *simvastatin, repaglinide, atorvastatin*) from the blood into the hepatocyte. More than 41 genetic variations have been reported, but the most commonly tested variation is the *5 allele, which has decreased function. Individuals who carry this allele have reduced expression of OATP1B1, and their phenotype is either classified as decreased function

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(*1/*5) or poor function (*5/*5). Consequently, drugs transported by OATP1B1 (for example, *simvastatin*) are not able to enter the cell as efficiently and plasma concentrations increase, resulting in an increased risk of adverse effects (Figure 48.14). Lipophilic statins (*atorvastatin*, *lovastatin*, *simvastatin*) are better substrates for transporters, as compared with hydrophilic statins. *Simvastatin* has the most evidence with SLCO1B1 genetic variations, which have been strongly associated with increased risk of muscle myopathy, an adverse effect resulting from the higher plasma drug concentrations. CPIC guidelines recommend prescribing a lower dose of *simvastatin* or considering an alternative statin in patients with decreased or poor SLCO1B1 function. The FDA Table of Pharmacogenetic Associations acknowledges the higher risk of myopathy in individuals with decreased transporter function, and this risk is higher when the 80-mg dose is used, as compared with lower dosages. A warning in the product labeling directs providers away from initiating simvastatin 80 mg, so less patients are now prescribed this high dose.

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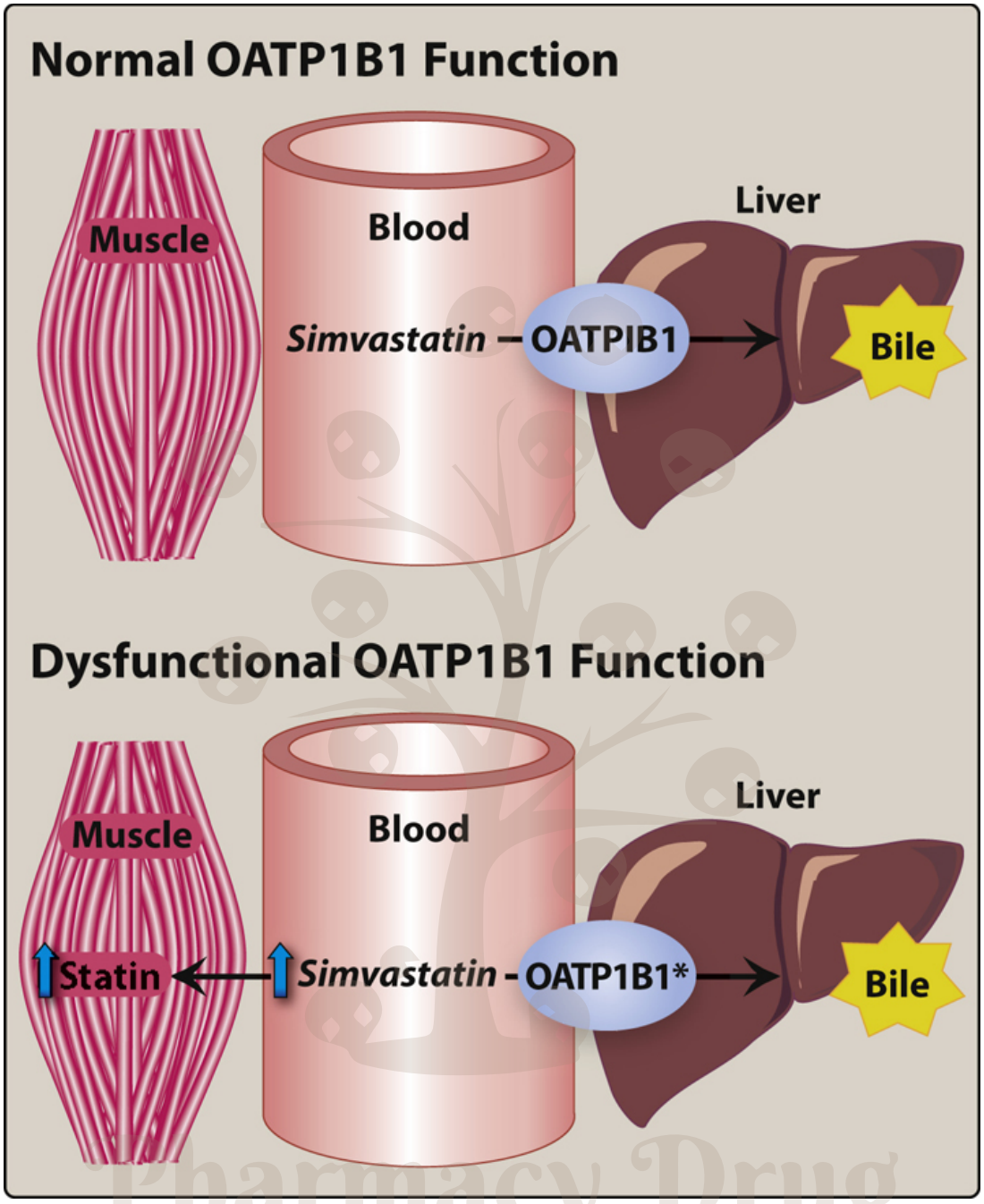

Figure 48.14 *Simvastatin* is transported by OATP1B1 into the liver.Decreased OATP1B1 function results in increased concentrations of *simvastatin* in the blood, leading to increased risk of adverse effects.Source: From the Centers for Disease Control and Prevention, Genomics and Precision Health Topics, Pharmacogenomics. Available at https://www.cdc.gov/genomics/disease/pharma.htm.

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2.OATP1A2: Transporters located within the intestine help with drug absorption. OATP1A2 is an influx transporter responsible for moving molecules, like *fexofenadine*, from the intestinal lumen into the endothelial cell of the intestine, which then allows the drug to get into the blood and be absorbed. Genetic polymorphisms that result in decreased OATP1A2 activity reduce the ability of the drug to get through the intestine to the blood, and, consequently, result in decreased absorption and lower drug concentrations. For example, *fexofenadine* would be expected to have reduced efficacy in the presence of decreased OATP1A2 activity because of the lower drug concentration. In addition to genetic polymorphisms, other substances can inhibit transporters and cause a similar effect. For example, there is a known drug interaction between *fexofenadine* and grapefruit juice. This is a transporter-mediated drug interaction. Grapefruit juice inhibits OATP1A2, so if consumed while taking *fexofenadine*, decreased blood concentrations of *fexofenadine* would be observed, as compared to *fexofenadine* taken alone.

V. HYPERSENSITIVITY REACTIONS

Not all pharmacogenomic implications are related to drug-metabolizing enzymes and transporters. Some variations in certain genes are associated with increased risk for life-threatening adverse drug reactions, independent of drug concentration. For these pharmacogenetic findings, genotype and phenotype results are reported in a way that indicates positive (carrying one or two copies) or negative (carrying no copies) for the variants of interest.

A. Human leukocyte antigen

Human leukocyte antigen (HLA) genes are part of the human major histocompatibility (MHC) gene complex. They encode cell surface proteins that present intracellular antigens to the immune system, enabling the immune system to distinguish self-proteins

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from foreign proteins. When foreign proteins are identified, an immune response is triggered. HLA genes are some of the most highly polymorphic genes in the human genome. Genetic variation in HLA genes is associated with cutaneous adverse reactions with the use of certain drugs. HLA genetic results are reported as "HLA*##:##," where the "#" are replaced with a four or six-digit identifier that indicates the allele type and specific protein subtype.

Two important HLA variants associated with drug-induced cutaneous reactions are HLA-B*15:02 and HLA-A:*31:01. HLA-B*15:02 is seen more frequently in East Asian (6.9%), Oceanian (5.4%), and South/Central Asian (4.6%) populations. HLA-B*15:02 frequency is much lower in Japanese (<1%) and Korean (<2.5%) populations. In contrast, HLA-A*31:01 is seen with the highest frequency in Japanese (8%), Hispanic/South Americans (6%), South Koreans (5%), and Caucasians (3%). While the frequencies can help determine broad population risk, this information cannot be substituted for individualized genotyping.

1.Carbamazepine: *Carbamazepine* is an anticonvulsant used for the treatment of epilepsy and other neurological disorders. While some *carbamazepine*-induced adverse effects are dose or concentration dependent (for example, dizziness or ataxia), other adverse drug reactions, such as cutaneous hypersensitivity reactions, have a more complex dose–response relationship and an immune-related etiology.

HLA-B*15:02 is linked with the risk for developing *carbamazepine*-induced Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). SJS/TEN is a group of potentially fatal cutaneous reactions involving epidermal detachment. The classification for SJS is up to 10% of body surface area (BSA) involvement, while TEN is greater than 30% BSA. Mortality rates for TEN can be as high as 30% or more, with sepsis being the most frequent cause of death. Based on the seriousness of the adverse reaction and strong

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evidence linking HLA-B*15:02 to *carbamazepine*-induced SJS/TEN, the product labeling for *carbamazepine* includes a boxed warning that patients carrying the HLA-*15:02 allele should not be treated with *carbamazepine* unless the benefits clearly outweigh the risks. The HLA-A*31:01 allele is associated with an increased risk for *carbamazepine*-induced SJS/TEN, maculopapular exanthema (MPE), and drug reaction with eosinophilia and system symptoms (DRESS). Both MPE and DRESS are hypersensitivity reactions characterized by generalized cutaneous eruptions. DRESS is the more severe reaction with systemic manifestations that can be life-threatening.

For patients who are HLA-B*15:02 and/or HLA-A*31:01 carriers, CPIC guidelines suggest that *carbamazepine* should be avoided if other agents are available (strong recommendation). If there are no alternatives available, *carbamazepine* use may be considered with more frequent clinical monitoring, and use should be discontinued at the first sign of a cutaneous adverse event. It is important to note that *oxcarbazepine*, the keto-analog of *carbamazepine*, also has a greater risk for drug-induced SJS/TEN in HLA-B*15:02 positive patients. The CPIC guidelines recommend against the use of *oxcarbazepine* in these patients (strong recommendation).

2.Phenytoin: HLA-B*15:02 is also associated with *phenytoin*-induced SJS and TEN. *Phenytoin* and *fosphenytoin* (prodrug of *phenytoin* generally used in emergency situations) are anticonvulsants used in the treatment of various seizure disorders. Use of *phenytoin* has declined due to the complex dosing, high rates of adverse effects, and the multitude of drug–drug interactions (see Chapter 19). Similar to *carbamazepine*, *phenytoin* has a mixture of dose-related adverse effects, including sedation and cognitive impairment, as well as non-dose-related allergic reactions, ranging from mild eruptions to life-threatening hypersensitivity reactions. CPIC guidelines recommend against the use of *phenytoin* or

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fosphenytoin in patients who are *phenytoin*-naïve and positive for the HLA-B*15:02 allele, unless the benefits clearly outweigh the risks (strong recommendation).

Of note, *phenytoin* is also impacted by genetic variation in CYP2C9. *Phenytoin* is a narrow therapeutic index drug, and reduced CYP2C9 enzyme activity is associated with higher plasma concentrations, which can increase the risk for *phenytoin*-related toxicity. CPIC guidelines recommend 25% and 50% lower maintenance dosing in CYP2C9 IMs with an AS of 1 and CYP2C9 PMs, respectively (IM moderate recommendation, PM strong recommendation). Subsequent dosing should be adjusted according to therapeutic dose monitoring, response, and adverse effects.

Clinical Application 48.3: Use of Phenytoin Based on Genetic Results

A 37-year-old woman was recently diagnosed with focal seizures. She is otherwise healthy and takes no medications. The neurologist wants to start her on *phenytoin.* Pharmacogenomic results are as follows: HLA-B*15:02 positive, HLA-A*31:01 negative, CYP2C9*1/*3. This patient is a carrier for the HLA-B*15:02 allele and is, therefore, at an increased risk for *phenytoin*-induced SJS/TEN. As such, *phenytoin* should be avoided in this individual if the benefit does not outweigh the risk, especially if alternative agents are available. Of note, *carbamazepine* and *oxcarbazepine* are inappropriate alternatives for the same reason. If the patient had been both HLA-B*15:02 and HLA-A*31:01 negative, *phenytoin* could be used, and the CYP2C9 result should be considered. CYP2C9*1/*3 is a combination of a normal function allele (activity value 1) and a no function allele (activity value 0), which is given an activity score of 1 and translates to an intermediate metabolizer. Per the CPIC guidelines, *phenytoin* should be administered using a typical initial or loading dose for the first dose. The maintenance dose should be reduced by 25%, with subsequent doses adjusted according to therapeutic drug monitoring, response, and adverse effects, including monitoring for *phenytoin*-induced SJS/TEN.

B. RYR1

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The RYR1 gene encodes the ryanodine receptor isoform 1 protein (RYR1), a subunit of the homotetrameric calcium release channel embedded in the sarcoplasmic reticulum membrane. RYR1-mediated calcium release plays an important role in excitation–contraction coupling in skeletal muscle fibers. Depolarization of the sarcolemma causes calcium release from the sarcoplasmic reticulum and triggers muscle contraction. Variants in the RYR1 gene predispose individuals to malignant hyperthermia susceptibility (MHS), a severe and sometimes lethal hypermetabolic reaction to halogenated volatile anesthetic agents (*sevoflurane*, *isoflurane*, *desflurane*; see Chapter 20) and the depolarizing muscle relaxant *succinylcholine.* For patients with MHS, exposure to any of the halogenated volatile anesthetics or *succinylcholine* can lead to sustained increase of cytoplasmic calcium within skeletal muscle fibers, resulting in uncontrolled muscle contractions. Malignant hyperthermia (MH) can lead to metabolic and respiratory acidosis, hyperkalemia, hyperthermia, arrhythmia, and, if not properly treated, cardiac arrest and death. There are over 50 identified variants in the RYR1 gene with varying levels of evidence to support pathogenicity, meaning they increase susceptibility to MH. Pathogenic variation in the RYR1 gene is responsible for about 70% of individuals with MHS. Current evidence strongly suggests that MHS pathogenic variants cause RYR1 channels to be hypersensitive to activation; however, the exact mechanism is still unknown. Use of halogenated volatile anesthetics or *succinylcholine* is relatively contraindicated in those with MHS. CPIC recommends these agents should only be used in extreme circumstances when the benefits outweigh the risks (strong recommendation). For those with uncertain susceptibility, CPIC recommends that clinical findings, family history, further genetic testing, and other laboratory data should guide use of these agents (strong recommendation).

VI. IMPLEMENTATION

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As described throughout the chapter, several gene–drug pairs are ready for clinical implementation, while others require additional evidence. Currently, clinical pharmacogenomics is primarily being implemented in large academic institutions but is steadily expanding across different practice settings. While widespread adoption of pharmacogenomics into clinical care has been somewhat slow, pharmacogenomics holds the promise to improve patient care and optimize drug use by improving efficacy and decreasing toxicity. The clinical impact of pharmacogenomics will continue to grow as research advances and new gene–drug pairs are discovered, or existing data are strengthened (Figure 48.15).

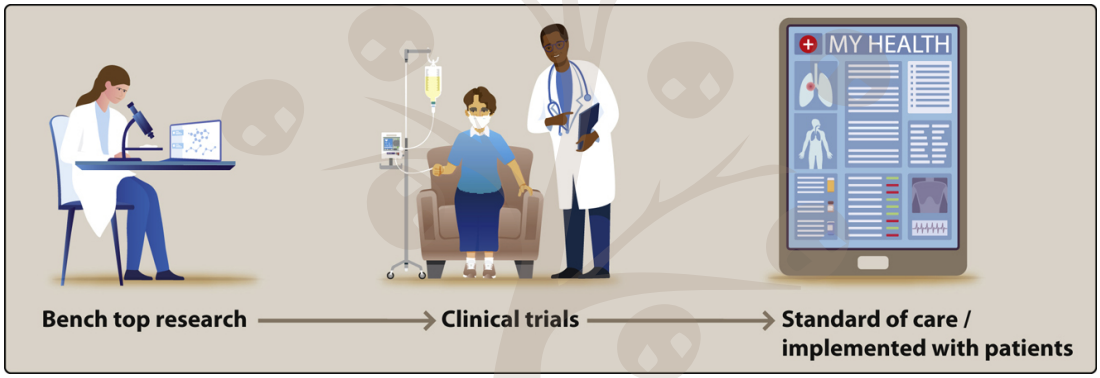

Figure 48.15 Genetic variations are often discovered in the laboratory, and the effect on medications must then be studied in clinical trials to determine the consequences of the variations and linkage to clinical outcomes.Once evidence is established, acting on the genetic variation in clinical practice can be implemented, and it may eventually become the standard of care.Modified from C. D.Klaassen . *Casarett and Doull's Toxicology*: The Basic Science of Poisons, 9th ed. McGraw-Hill Education.

Chapter Summary

- Pharmacogenomics is the study of the impact of genetic variation on drug response; it can help improve drug use through tailoring dosing and drug

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selection to the individual.

- *Clopidogrel* is a prodrug that requires functional CYP2C19 enzyme activity to be activated and exert its pharmacological effect; CYP2C19 PMs and IMs are at risk for pharmacotherapy failure.
- Variation in CYP2D6 enzyme activity can alter the safety and efficacy of certain opioids (*codeine*, *tramadol*, and, to a lesser extent, *hydrocodone*).
- Many SSRIs are metabolized primarily by CYP2C19 or CYP2D6, and genetic results can predict if the individual is at risk for pharmacotherapy failure or increased risk for adverse effects.
- *Warfarin* dose requirements are impacted by pharmacogenetic variations, particularly in CYP2C9 and VKORC1.
- NSAIDs are metabolized by CYP2C9 to inactive metabolites. For NSAIDs with longer half-lives (*meloxicam*, *piroxicam*), an alternative should be considered in CYP2C9 PMs.
- Genetic variation in transporters can impact the pharmacokinetics of certain drugs. *Simvastatin* and SLCO1B1 is a key example where reduced expression of a drug transporter (OATP1B1) results in higher plasma concentrations and can lead to adverse effects such as myopathy.
- HLA-B*15:02 is associated with an increased risk for *carbamazepine*-, *oxcarbazepine*-, and *phenytoin*-induced hypersensitivity reactions.
- HLA-A*31:01 is associated with an increased risk for *carbamazepine*-induced hypersensitivity reactions.
- Pathogenic variants in RYR1 predispose an individual to MHS, a potentially life-threatening reaction to halogenated volatile anesthetics and the depolarizing skeletal muscle agent *succinylcholine.*

STUDY QUESTIONS

Choose the ONE best answer.

48.1 Which professional organization creates guidelines for the use of pharmacogenomic results in clinical care?

A. FDA
B. CPIC
C. AMP
D. PharmVar

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Correct answer = B. The Clinical Pharmacogenetics Implementation Consortium (CPIC) creates guidelines for the use of pharmacogenomic results in clinical care. A, C, and D are incorrect because these resources do not create guidelines centered on using pharmacogenomics in clinical care. The FDA does include some pharmacogenomic information in package labeling, but does not provide specific guidance. AMP does create guidelines, but they are centered on specific alleles that should be included in genotyping.

48.2 A combination of two no-function alleles translates to what type of drug-metabolizing enzyme phenotype?

A. Poor metabolizer
B. Intermediate metabolizer
C. Normal metabolizer
D. Rapid metabolizer

Correct answer = A. Two no-function alleles translates to a poor metabolizer. B, C, and D are incorrect because these phenotypes are created by different combinations of alleles that include at least one allele that is not a no-function allele.

48.3 A 58-year-old man just had a bare metal stent placed. He is prescribed clopidogrel and aspirin, in addition to other medications. CYP2C19 results indicated a genotype of *2/*2. Which of the following is correct regarding his clopidogrel prescription?

A. CYP2C19 will activate clopidogrel as expected, it is appropriate to continue clopidogrel.
B. CYP2C19 will activate clopidogrel more than expected, it is appropriate to continue clopidogrel.
C. CYP2C19 will activate clopidogrel less than expected, it is not appropriate to continue clopidogrel.
D. CYP2C19 will activate clopidogrel less than expected, it is appropriate to continue clopidogrel.

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Correct answer = C. CYP2C19 *2/*2 translates to being a poor metabolizer, and having little to no enzyme activity. Therefore, clopidogrel will not be able to be activated by CYP2C19, and the drug is not expected to have therapeutic effects. An alternative should be selected.

48.4 A 30-year-old woman is diagnosed with depression, and her provider wants to initiate an SSRI. Her genotype results are as follows: CYP2C19 *1/*17, CYP2D6 *1/*4. Which of the following SSRIs would be best to initiate?

A. Citalopram
B. Escitalopram
C. Paroxetine
D. Sertraline

Correct answer = C. Citalopram, escitalopram, and sertraline are all metabolized by CYP2C19 and the patient is a rapid metabolizer, which may put her at risk for therapeutic failure with these SSRIs. While it would be reasonable to initiate sertraline and then change to an alternative if not responding, her CYP2D6 results make paroxetine a better option. The CYP2D6 results indicate she is an intermediate metabolizer, but no dose adjustments are recommended in this population.

48.5 Which of the following is primarily responsible for the analgesic effects of tramadol?

A. Morphine
B. Tramadol
C. Oxymorphone
D. O-desmethyltramadol

POLE STAR

Correct answer = D. O-desmethyltramadol is more potent than tramadol and is the primary metabolite responsible for the analgesic effects of tramadol. A and C are incorrect because morphine is a metabolite of codeine and oxymorphone is a metabolite of oxycodone.

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48.6 Which of the following statements is correct regarding warfarin pharmacogenetics?

A. Reduced CYP2C9 enzyme activity is associated with increased warfarin sensitivity and may result in requiring lower doses.
B. Reduced CYP2C9 enzyme activity is associated with decreased warfarin sensitivity and may result in requiring higher doses.
C. It is appropriate to use a pharmacogenetic guided warfarin dosing for an African American who had CYP2C9 testing by a lab that only detected *2 and *3 alleles.
D. The CYP2C9 *5, *6, *8, and *11 alleles are highly frequent among all ethnic groups.

Correct answer = A. Warfarin is metabolized by CYP2C9 into inactive metabolites. If CYP2C9 enzyme activity is reduced, there is more warfarin available to inhibit VKORC1, which would make the individual more sensitive to warfarin and require lower doses. The CYP2C9 *5, *6, *8, and *11 alleles are only frequent among African Americans and not those of European ancestry. Since these alleles are frequent in African Americans, they must be tested for in order to use a pharmacogenetic guided warfarin approach in this population.

48.7 Which of the following CYP2C9-NSAID recommendations are correct?

A. Celecoxib—choose alternative in a CYP2C9 poor metabolizer
B. Meloxicam—choose alternative in a CYP2C9 poor metabolizer
C. Piroxicam—reduce the dose by 50% in a CYP2C9 intermediate metabolizer with an AS of 1.0
D. Ibuprofen—reduce the dose by 50% in a CYP2C9 normal metabolizer

Correct answer = B. The recommendation for celecoxib is to lower the dose by 25% to 50% in a PM per CPIC and FDA. The recommendation for meloxicam is to choose an alternative not metabolized by CYP2C9 in a CYP2C9 PM. The

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recommendation for piroxicam is to choose an alternative not metabolized by CYP2C9 in a CYP2C9 IM with an AS of 1.0. There are no recommendations to change from standard therapy in CYP2C9 NMs for ibuprofen.

48.8 A 61-year-old man with hypertension, hyperlipidemia, and diabetes is currently prescribed simvastatin, lisinopril, HCTZ, and metformin. He presents to his provider complaining of muscle pain, and his provider orders SLCO1B1 genotyping, which comes back as *5/*5. Which of the following medication adjustments is most appropriate for this patient?

A. No changes are warranted.
B. Simvastatin dose should be lowered or an alternative such as rosuvastatin should be prescribed in its place.
C. Simvastatin dose should be increased.
D. Patient should be monitored, but no changes are warranted until blood work is completed.

Correct answer = B. Simvastatin is transported into the liver by SLCO1B1. The *5/*5 genotype indicates poor function, and CPIC recommends a lower dose of simvastatin or an alternative statin such as pravastatin or rosuvastatin.

48.9 Which of the following is associated with an increased risk for phenytoin-induced hypersensitivity reactions?

A. CYP2D6
B. CYP2C19
C. HLA-B*15:02
D. HLA-A*31:01

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Correct answer = C. A and B are incorrect because they have no role with phenytoin adverse effects. D is incorrect because it is associated with carbamazepine-induced hypersensitivity reactions.

48.10 Which of the following best describes the relationship between RYR1 variants and succinylcholine?

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A. RYR1 poor metabolism leads to increased plasma concentrations of succinylcholine, leading to MHS.
B. RYR1 ultrarapid metabolism leads to decreased plasma concentrations of succinylcholine, leading to decreased efficacy.
C. Pathogenic variants in RYR1 may cause sustained increase of cytoplasmic calcium within skeletal muscle fibers, leading to uncontrolled muscle contractions.
D. Pathogenic variants are associated with an increased risk for succinylcholine-induced SJS/TEN.

Correct answer = C. A and B are incorrect because RYR1 is not related to succinylcholine plasma concentrations. D is incorrect because RYR1 is not associated with succinylcholine-induced SJS/TEN.

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